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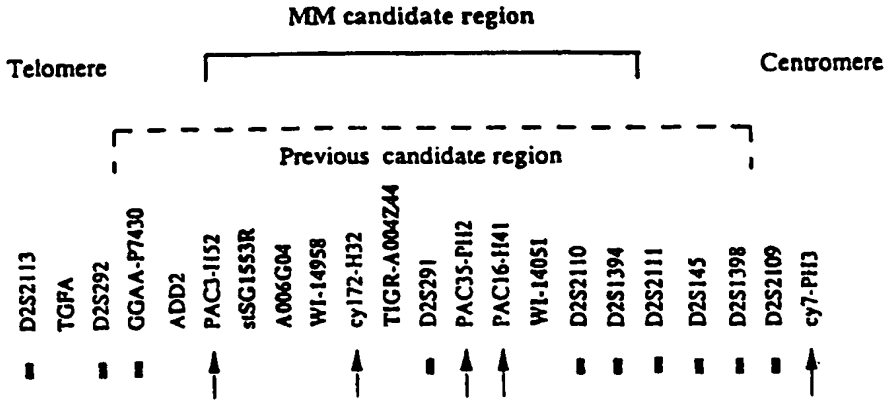

(57) Abstract

A novel gene and the protein encoded therein, i.e., dysferlin, are disclosed. This gene and its expression products are associated with muscular dystrophy, e.g., Miyoshi myopathy and limb girdle muscular dystrophy 2B.

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DYSFERLIN, A GENE MUTATED IN DISTAL MYOPATHY AND LIMB GIRDLE MUSCULAR DYSTROPHY

RELATED APPLICATION INFORMATION

This application claims priority from provisional application serial no. 60/097,927, filed August 25, 1998.

Statement as to Federally Sponsored Research

The work described herein was supported in part by NIH grants 5P01AG12992, 5R01N834913A, and 5P01NS31248. The Federal Government therefore may have certain rights in the invention.

Background of the Invention

The invention relates to genes involved in the onset of muscular dystrophy.

Muscular dystrophies constitute a heterogeneous group of disorders. Most are characterized by weakness and atrophy of the proximal muscles, although in rare myopathies such as "Miyoshi myopathy" symptoms may first arise in distal muscles. Of the various hereditary types of muscular dystrophy, several are caused by mutations or deletions in genes encoding individual components of the dystrophin-associated protein (DAP) complex. It is this DAP complex that links the cytoskeletal protein dystrophin to the extracellular matrix protein, laminin-2.

Muscular dystrophies may be classified according to the gene mutations that are associated with specific clinical syndromes. For example, mutations in the gene encoding the cytoskeletal protein dystrophin result in either Duchenne's Muscular Dystrophy or Becker's Muscular Dystrophy, whereas mutations in the gene encoding the extracellular matrix protein merosin produce Congenital

Muscular Dystrophy. Muscular dystrophies with an autosomal recessive mode of inheritance include "Miyoshi myopathy" and the several limb-girdle muscular dystrophies (LGMD2). Of the limb-girdle muscular dystrophies, the deficiencies resulting in LGMD2C, D, E, and F result from mutations in genes encoding the membrane-associated sarcoglycan components of the DAP complex.

Summary of the Invention

A novel protein, designated dysferlin, is identified and characterized. The dysferlin gene is normally expressed in skeletal muscle cells and is selectively mutated in several families with the hereditary muscular dystrophies, *e.g.*, Miyoshi myopathy (MM) and limb girdle muscular dystrophy-2B (LGMD2B). These characteristics of dysferlin render it a candidate disease gene for both MM and LGMD2B. An additional novel protein, brain-specific dysferlin, has also been identified. Defects in brain-specific dysferlin may predispose to selected disorders of the central nervous system. Moreover, the expression of brain-specific dysferlin may be important as a marker for normal neural development (e.g., *in vivo* or in neural cells in culture). Manipulation of levels of expression of brain-specific dysferlin, and of the type of expressed brain-specific dysferlin is of use for analyzing the function of brain-specific dysferlin and related dysferlin-associated molecules.

The invention features an isolated DNA which includes a nucleotide sequence hybridizing under stringent hybridization conditions to a strand of SEQ ID NO:3 or SEQ ID NO:117.

The invention also features an isolated DNA including a nucleotide sequence selected from SEQ ID NOs:4-12.

Also within the invention is an isolated DNA comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:22-30.

Also within the invention is a single stranded oligonucleotide of 14-50 nucleotides in length having a nucleotide sequence identical to a portion of a strand of SEQ ID NO:3.

Also within the invention is a pair of PCR primers consisting of:

(a) a first single stranded oligonucleotide consisting of 14-50 contiguous nucleotides of the sense strand of SEQ ID NO:117; and

(b) a second single stranded oligonucleotide consisting of 14-50 contiguous nucleotides of the antisense strand of SEQ ID NO:117, wherein the sequence of at least one of the oligonucleotides is identical to a portion of a strand of SEQ ID NO:3, and the first oligonucleotide is not complementary to the second oligonucleotide.

Also within the invention is a pair of single stranded oligonucleotides selected from of SEQ ID NOs 130-231, SEQ ID NO:110, and SEQ ID NO:112.

Also within the invention is an isolated DNA including a nucleotide sequence that encodes a protein that shares at least 70% sequence identity with SEQ ID NO:2, or a complement of the nucleotide sequence.

Also within the invention is an isolated DNA including a nucleotide sequence which hybridizes under stringent hybridization conditions to a strand of a nucleic acid, the nucleic acid having a sequence selected from SEQ ID NOs:31-79 and 90-101.

Also within the invention is a single stranded oligonucleotide of 14-50 nucleotides in length having a nucleotide sequence which is identical to a portion of a strand of a nucleic acid selected from SEQ ID NOs:31-79 and 90-100.

Also within the invention is a pair of PCR primers consisting of:

(a) a first single stranded oligonucleotide consisting of 14-50 contiguous nucleotides of the sense strand of a nucleic acid selected from SEQ ID NOs:31-85; and

(b) a second single stranded oligonucleotide consisting of 14-50 contiguous nucleotides of the antisense strand of a nucleic acid selected from SEQ ID NOs:31-85, wherein the sequence of at least one of the oligonucleotides includes a sequence identical to a portion of a strand of a nucleic acid selected from SEQ ID NOs: 31-79 and 90-100, and the first oligonucleotide is not complementary to the second oligonucleotide.

Also within the invention is a pair of single stranded oligonucleotides selected from SEQ ID NOs 101-116, SEQ ID NOs 184-185, SEQ ID NOs 188-191, SEQ ID NOs 210-213, and SEQ ID NOs 216-217.

Also within the invention is a substantially pure protein that has an amino acid sequence sharing at least 70% sequence identity with SEQ ID NO:2.

Also within the invention is a substantially pure protein the sequence of which includes amino acid residues 1-500, 501-1000, 1001-1500, or 1501-2080 of SEQ ID NO:2.

Also within the invention is a substantially pure protein including the amino acid sequence of SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, or SEQ ID NO:89.

In another aspect, the invention features a transgenic non-human mammal having a transgene disrupting

or interfering with the expression of a dysferlin gene, the transgene being chromosomally integrated into the germ cells of the animal.

Another embodiment of the invention features a method of decreasing the symptoms of muscular dystrophy in a mammal by introducing into a cell of the mammal (e.g., a muscle cell or a muscle precursor cell) an isolated DNA which hybridizes under stringent hybridization conditions to a strand of SEQ ID NO:3.

Another aspect of the invention provides a method for identifying a patient, a fetus, or a pre-embryo at risk for having a dysferlin-related disorder by (a) providing a sample of genomic DNA from the patient, fetus, or pre-embryo; and (b) determining whether the sample contains a mutation in a dysferlin gene.

In another aspect, the invention provides a method for identifying a patient, a fetus, or a pre-embryo at risk for having a dysferlin-related disorder by (a) providing a sample including dysferlin mRNA from the patient, fetus, or pre-embryo; and (b) determining whether the dysferlin mRNA contains a mutation.

Methods of identifying mutations in a dysferlin sequence are useful for predicting (e.g., predicting whether an individual is at risk for developing a dysferlin-related disorder) or diagnosing disorders associated with dysferlin, e.g., MM and LGMD2B. Such methods can also be used to determine if an individual, fetus, or a pre-embryo is a carrier of a dysferlin mutation, for example in screening procedures. Methods which distinguish between different dysferlin alleles (e.g., a mutant dysferlin allele and a normal dysferlin allele) can be used to determine carrier status.

The invention also features an isolated nucleic acid comprising a nucleotide sequence which hybridizes under stringent hybridization conditions to nucleic acids

3284-3720 of SEQ ID NO:232, or the complement of the nucleotide sequence. An isolated nucleic acid including a nucleotide sequence identical to the sequence of nucleotides 3284-3720 of SEQ ID NO:232, or a complement of the nucleotide sequence is also a feature of the invention. The isolated nucleic acid can include the entire sequence of SEQ ID NO:232 or the complement of SEQ ID NO:232.

Another aspect of the invention features an isolated polypeptide that includes: a) at least 15 contiguous amino acids of the polypeptide comprising amino acids 1-24 of SEQ ID NO:233, b) a naturally occuring allelic variant of a polypeptide comprising amino acids 1-24 of SEQ ID NO:233, or c) an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes under stringent conditions to nucleotides 3284-3720 of SEQ ID NO:232. The polypeptide of this aspect can include the entire sequence of SEQ ID NO:233.

Also included in the invention is a vector comprising the nucleic acid of claim 44 and a cell that contains the vector. Another aspect of the invention features a method of making a polypeptide by culturing the cell which contains the vector.

The invention also features an antibody which specifically binds to a polypeptide of such as those described above. The antibody can bind to a polypeptide selected from amino acids 253-403 of SEQ ID NO:233, amino acids 624-865 of SEQ ID NO:233, and amino acids 1664-1786 of SEQ ID NO:233. Antibodies of the invention can be monclonal or polyclonal antibodies.

An "isolated DNA" is DNA which has a naturally occurring sequence corresponding to part or all of a given gene but is free of the two genes that normally flank the given gene in the genome of the organism in

which the given gene naturally occurs. The term therefore includes a recombinant DNA incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote. It also includes a separate molecule such as a cDNA, a genomic fragment, a fragment produced by polymerase chain reaction (PCR), or a restriction fragment, as well as a recombinant nucleotide sequence that is part of a hybrid gene, i.e., a gene encoding a fusion protein. The term excludes intact chromosomes and large genomic segments containing multiple genes contained in vectors or constructs such as cosmids, yeast artificial chromosomes (YACs), and P1-derived artificial chromosome (PAC) contigs.

A "noncoding sequence" is a sequence which corresponds to part or all of an intron of a gene, or to a sequence which is 5′ or 3′ to a coding sequence and so is not normally translated.

An expression control sequence is "operably linked" to a coding sequence when it is within the same nucleic acid and can control expression of the coding sequence.

A "protein" or "polypeptide" is any chain of amino acids linked by peptide bonds, regardless of length or post-translational modification, e.g., glycosylation or phosphorylation.

As used herein, the term "percent sequence identity" means the percentage of identical subunits at corresponding positions in two sequences when the two sequences are aligned to maximize subunit matching, i.e., taking into account gaps and insertions. For purposes of the present invention, percent sequence identity between two polypeptides is to be determined using the Gap program and the default parameters as specified therein. The Gap program is part of the Sequence Analysis Software

Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705.

The algorithm of Myers and Miller, CABIOS (1989) can also be used to determine whether two sequences are similar or identical. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

As used herein, the term "stringent hybridization conditions" means the following DNA hybridization and wash conditions: hybridization at 60°C in the presence of 6 x SSC, 0.5% SDS, 5 x Denhardt's Reagent, and 100 μg/ml denatured salmon sperm DNA; followed by a first wash at room temperature for 20 minutes in 0.5 x SSC and 0.1% SDS and a second wash at 55°C for 30 minutes in 0.2 x SSC and 0.1% SDS.

A "substantially pure protein" is a protein separated from components that naturally accompany it. The protein is considered to be substantially pure when it is at least 60%, by dry weight, free from the proteins and other naturally-occurring organic molecules with which it is naturally associated. Preferably, the purity of the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight. A substantially pure dysferlin protein can be obtained, for example, by extraction from a natural source, by expression of a recombinant nucleic acid encoding a dysferlin polypeptide, or by chemical synthesis. Purity can be measured by any appropriate method, e.g., column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis. A chemically synthesized protein or a recombinant protein produced in a cell type other than

the cell type in which it naturally occurs is, by definition, substantially free from components that naturally accompany it. Accordingly, substantially pure proteins include those having sequences derived from eukaryotic organisms but which have been recombinantly produced in *E. coli* or other prokaryotes.

An antibody that "specifically binds" to an antigen is an antibody that recognizes and binds to the antigen, e.g., a dysferlin polypeptide, but which does not substantially recognize and bind to other molecules in a sample (e.g., a biological sample) which naturally includes the antigen, e.g., a dysferlin polypeptide. An antibody that "specifically binds" to dysferlin is sufficient to detect a dysferlin polypeptide in a biological sample using one or more standard immunological techniques (for example, Western blotting or immunoprecipitation).

A "transgene" is any piece of DNA, other than an intact chromosome, which is inserted by artifice into a cell, and becomes part of the genome of the organism which develops from that cell. Such a transgene may include a gene which is partly or entirely heterologous (i.e., foreign) to the host organism, or may represent a gene homologous to an endogenous gene of the organism.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention. The present materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present

specification, including definitions, will control. All the sequences disclosed in the sequence listing are meant to be double-stranded except the sequences of oligonucleotides.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

Brief Description of the Drawings

Fig. 1A is a physical map of the MM locus. Arrows indicate the five new polymorphic markers and filled, vertical rectangular boxes indicate the previously known polymorphic markers. The five ESTs that are expressed in skeletal muscle are highlighted in bold. Detailed information on the minimal tiling path of the PAC contig spanning the MM/LGMD2B region is provided in Liu et al., 1998, *Genomics* 49:23-29. The minimal candidate MM region is designated by the solid bracket (top) and compared to the previous candidate region (dashed bracket). TGFA and ADD2 are transforming growth factor alpha and β-adducin 2.

Fig. 1B is a representation of the dysferlin cDNA clones. The probes used in the three successive screens are shown in bold (130347, cDNA10, A27-F2R2). The two most 5′ cDNA clones are also shown (B22, B33). The 6.9 kb cDNA for dysferlin (SEQ ID NO:1) is illustrated at the bottom with start and stop codons as shown.

Fig. 1C is a representation of the predicted dysferlin protein. The locations of four C2 domains (SEQ ID NOs: 86-89) are indicated by stippled boxes, while the putative transmembrane region is hatched. Vertical lines above the cDNA denote the positions of the mutations in Table 2; the associated labels indicate the phenotypes (MM - Miyoshi myopathy; LGMD - limb girdle

muscular dystrophy; DMAT - distal myopathy with anterior tibial onset).

Fig. 2 is the sequence of the predicted 2,080 amino acids of dysferlin (SEQ ID NO:2). The predicted membrane spanning residues are in bold at the carboxy terminus (residues 2047-2063). Partial C2 domains are underlined. Bold, underlined sequences are putative nuclear targeting residues. Possible membrane retention sequences are enclosed within a box.

Fig. 3 is a comparison of the Kyle-Doolittle hydrophobicity plots of the dysferlin protein and fer-1. On the Y-axis, increasing positivity corresponds to increasing hydrophobicity. Both proteins have a single, highly hydrophobic stretch at the carboxy terminal end (arrow). Both share regions of relative hydrophilicity approximately at residue 1,000 (arrowhead).

Fig. 4 is a SSCP analysis of a representative pedigree with dysferlin mutations. Each member of the pedigree is illustrated above the corresponding SSCP analysis. For each affected individual (solid symbols) shifts are evident in alleles 1 and 2, corresponding respectively to exons 36 and 54. As indicated, the allele 1 and 2 variants are transmitted respectively from the mother and the father. The two affected daughters in this pedigree have the limb girdle muscular dystrophy (LGMD) phenotype while their affected brother has a pattern of weakness suggestive of Miyoshi myopathy (MM).

Fig. 5 is a representation of the genomic structure of dysferlin. The 55 exons of the dysferlin gene and their corresponding SEQ ID NOs are indicated below the 6911 bp cDNA (solid line). The cDNA sequences corresponding to SEQ ID NO:1 and SEQ ID NO:3 are shown relative to the 6911 bp cDNA.

Figs. 6A-B are the cDNA sequence of brain-specific dysferlin (SEQ ID NO:232) and the predicted amino acid

sequence (in single-letter code) of brain-specific dysferlin (SEQ ID NO:233).

Detailed Description

The Miyoshi myopathy (MM) locus maps to human chromosome 2p12-14 between the genetic markers D2S292 and D2S286 (Bejaoui et al., 1995, *Neurology* 45:768-72). Further refined genetic mapping in MM families placed the MM locus between markers GGAA-P7430 and D2S2109 (Bejaoui et al., 1998, *Neurogenetics* 1:189-96). Independent investigation has localized the limb-girdle muscular dystrophy (LGMD-2B) to the same genetic interval (Bashir et al., 1994, *Hum. Molec. Genetics* 3:455-57; Bashir et al., 1996, *Genomics* 33:46-52; Passos-Bueno et al., 1995, *Genomics* 27:192-95). Furthermore, two large, inbred kindreds have been described whose members include both MM and LGMD2B patients (Weiler et al., 1996, *Am. J. Hum. Genet.* 59:872-78; Illarioshkin et al., 1997, *Genomics* 42:345-48). In these familial studies, the disease gene(s) for both MM and LGMD2B mapped to essentially the same genetic interval. Moreover, in both pedigrees, individuals with MM or LGMD2B phenotypes share the same haplotypes. This raises the intriguing possibility that the two diseases may arise from the same gene defect and that a particular disease phenotype is the result of modification by additional factors.

A 3-Mb PAC contig spanning the entire MM/LGMD2B candidate region was recently constructed to facilitate the cloning of the MM/LGMD2B gene(s) (Liu et al., 1998, *Genomics* 49:23-29). This high resolution PAC contig resolved the discrepancies of the order of markers in previous studies (Bejaoui et al., 1998, *Neurogenetics* 1:189-96; Bashir et al., 1996, *Genomics* 33:46-52; Hudson et al., 1995, *Science* 270:1945-54). The physical size of the PAC contig also indicated that the previous minimal

size estimation based on YAC mapping data was significantly underestimated.

Identification of Repeat Sequences and Repeat Typing

The PAC contig spanning the MM/LGMD2B region (Liu et al., 1998, *Genomics* 49:23-29) was used as a source for the isolation of new informative markers to narrow the genetic interval of the disease gene(s). DNA from the PAC clones spanning the MM/LGMD2B region was spotted onto Hybond N+™ membrane filters (Amersham, Arlington Heights, IL). The filters were hybridized independently with the following γ-^{32}P (Du Pont, Wilmington, DE) labeled repeat sequences: (1) $(CA)_{15}$; (2) pool of $(ATT)_{10}$, $(GATA)_8$ and $(GGAA)_8$; (3) pool of $(GAAT)_8$, $(GGAT)_8$ and $(GTAT)_8$; and (4) pool of $(AAG)_{10}$ and $(ATC)_{10}$. Hybridization and washing of the filters were carried out at 55°C following standard protocols (Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual* (2nd Edition), Cold Spring Harbor Press, N.Y.).

Miniprep DNAs of PAC clones containing repeat sequences were digested with restriction enzymes *Hind*III and *Pst*I and ligated into pBluescript II (KS+) vector which is (Stratagene, La Jolla, CA) digested with the same enzymes. Filters of the PAC subclones were hybridized to the γ-^{32}P labeled repeats that detected the respective PACs. For clones with an insert size greater than 1 kb the repeat sequences of which could not be identified by a single round of sequencing, the inserts were further subcloned by digestion with *Hae*III and ligation in *Eco*RV-digested pZero-2.1 vector (Invitrogen, Inc., Carlsbad, CA). Miniprep DNAs of the positive subclones were subjected to manual dideoxy sequencing with Sequenase™ enzyme (US Biochemicals, Inc., Cleveland, OH). Primer pairs for amplifying the repeat sequences were selected using the computer program Oligo (Version

4.0, National Biosciences, Inc., Plymouth, MN). Primer sequences are shown in Table 1.

TABLE 1

New Polymorphic Markers Mapped to the MM/LGMD2B Region

Marker	Repeat	Primers (5′ to 3′)	Annealing Tm (°C)	Size in PAC (bp)	No. of alleles[1]	Het[2]
PAC3-H52	CA	GATCTAACCCTGCTGCTCACC (SEQ ID NO:120) CTGGTGTGTTGCAGAGCGCTG (SEQ ID NO:121)	57	138	10	0.82
Cy172-H32[3]	CCAT	CCTCTCTTCTGCTGTCTTCAG (SEQ ID NO:122) TGTGTCTGGTTCCACCTTCGT (SEQ ID NO:123)	56	199	7	0.72
PAC35-PH2	CAT	TCCAAATAGAAATGCCTGAAC (SEQ ID NO:124) AGGTATCACCTCCAAGTGTTG (SEQ ID NO:125)	56	161	5	0.30
PAC16-H41	Complex	TACCAGCTTCAGAGCTCCCTG (SEQ ID NO:126) TTGATCAGGGTGCTCTTGG (SEQ ID NO:127)	58	280	4	0.41
Cy7-PH3	AAGG	GGAGAATTGCTTGAACCCAG (SEQ ID NO:128) TGGCTAATGATGTTGAACATTT (SEQ ID NO:129)	56	211	4	0.32

[1] Observed in 50 unrelated caucasians.
[2] Heterozygosity index.
[3] Located within intron 2 of the *dysferlin* gene.

All oligonucleotides were synthesized by Integrated DNA Technologies, Inc. (Coralville, IA). PCR typing of the repeat markers followed previously described protocols (Bejaoui et al., 1995, *Neurology* 45:768-772).

Identification of Repeat Markers and Haplotype Analysis

After hybridization with labeled repeat oligos, 17 different groups of overlapping PACs were identified that contained repeat sequences. Some groups contained previously identified repeat markers. For example, five groups of PACs were positively identified by a pool of repeat probes including $(ATT)_{10}$, $(GATA)_8$, and $(GGAA)_8$. Of these, three groups contained known markers GGAA-P7430 (GGAA repeat), D2S1394 (GATA repeat) and D2S1398 (GGAA repeat) (Hudson et al., 1992, *Nature* 13:622-29; Gastier et al., 1995, *Hum. Molecular Genetics* 4:1829-36). No attempt was made to isolate new repeat markers from these PACs and they were not further analyzed. Similarly, seven groups of PACs that contained known CA repeat markerswere excluded. Seven groups of PACs that contained unidentified repeats were retained for further analysis. For each group, the PAC containing the smallest insert was selected for subcloning. Subclones were re-screened and positive clones were sequenced to identify repeats. In total, seven new repeat sequences were identified within the MM/LGMD2B PAC contig. Of these, five are polymorphic within the population that was tested. The information for these five markers is summarized in Table 1. Based on the PAC contig constructed previously across the MM candidate locus (Liu et al., 1998, *Genomics* 48:23-29), the five new markers and ten previously published polymorphic markers were placed in an unambiguous order (Fig. 1).

These markers were analyzed in a large, consanguineous MM family (Bejaoui et al., 1995, *Neurology* 45: 768-72; Bejaoui et al., 1998, *Neurogenetics* 1:189-96). Because MM is a recessive condition, the locus can be defined by identifying regions of the genome that show homozygosity in affected individuals. Conversely, because of the high penetrance of this adult-onset

condition, unaffected adult individuals are not expected to be homozygous by descent across the region. Analysis of haplotype homozygosity in this pedigree indicates that the disease gene lies between markers D2S2111 and PAC3-H52. Based on the PAC mapping data, the physical distance for this interval is approximately 2.0 Mb. No recombination events were detected between four informative markers (markers cy172-H32 to PAC16-H41) and the disease locus in family MM-21 (Fig. 1A).

Identification of Five Muscle-Expressed ESTs

Twenty-two ESTs and two genes (transforming growth factor alpha [TGFα] and beta-adducin [ADD2]) were previously mapped to the MM/LGMD2B PAC contig (Fig. 1A) (Liu et al., 1998, *Genomics* 48:23-29). Two μl (approximately 0.1 ng/μl) of Marathon-ready™ skeletal muscle cDNA (Clontech, Palo Alto, CA) were used as template in a 10 μl PCR reaction for analysis of muscle expression of ESTs. The PCR conditions were the same as for the PCR typing of repeat markers. PCR analysis of skeletal muscle cDNA indicated that five of these ESTs (A006G04, stSG1553R, WI-14958, TIGR-A004Z44 and WI-14051) map within the minimal genetic MM interval of MM and are expressed in skeletal muscle.

Probes were selected corresponding to each of these five ESTs for Northern blot analysis. cDNA clones (130347, 48106, 172575, 184080, and 510138) corresponding to the five ESTs that are expressed in muscle (respectively TIGR-A004Z44, WI-14051, WI-14958, stSG1553R and A006G04) were selected from the UniGene database (http:/www.ncbi.nlm.nih.gov/UniGene/) and obtained from Genome Systems, Inc. (St. Louis, MO). The cDNA probes were first used to screen the MM/LGMD2B PAC filters to confirm that they mapped to the expected position in the MM/LGMD2B contig.

A Northern blot (Clontech) of multiple human tissues was sequentially hybridized to the five cDNA probes and a control β-actin cDNA at 65°C following standard hybridization and washing protocols (Sambrook et al., *supra*). Between hybridizations, probes were removed by boiling the blot at 95-100°C for 4-10 min with 0.5% SDS. The blot was then re-exposed for 24 h to confirm the absence of previous hybridization signals before proceeding with the next round of hybridization.

The tissue distribution, intensity of the signals and size of transcripts detected by the five cDNA probes varied. Probes corresponding to ESTs stSG1553R, TIGR-A004Z44 and WI-14958 detected strong signals in skeletal muscle. In addition, the cDNA corresponding to TIGR-A004Z44 detected a 3.6-3.8 kb brain-specific transcript instead of the 8.5 kb message that was present in other tissues. It is likely that these five ESTs correspond to different genes since the corresponding cDNA probes used for Northern analysis derive from the 3' end of messages, map to different positions in the MM/LGMD2B contig (Fig. 1A), and differ in their expression patterns.

Current database analysis suggests that three of these ESTs (stSG1553R, WI-14958 and WI-14051) do not match any known proteins (Schuler et al., 1996, Science 274:540-46). A006G04 has weak homology with a protein sequence of unknown function that derives from *C. elegans*. TIGR-A004Z44 has homology only to subdomains present within protein kinase C. Because the five genes corresponding to the ESTs are expressed in skeletal muscle and map within the minimal genetic interval of the MM/LGMD2B gene(s), they are candidate MM/LGMD2B gene(s).

Cloning of Dysferlin cDNA

EST TIGR-A004Z44 gave a particularly strong skeletal muscle signal on the Northern blot. Moreover, it is bracketed by genetic markers that show no recombination with the disease phenotype in family MM-21 (Fig. 1). The corresponding transcript was therefore cloned and analyzed as a candidate MM gene. From the Unigene database, a cDNA IMAGE clone (130347, 979 bp) was identified that contained the 483 bp EST TIGR-A004Z44.

Approximately 1 x 10^6 recombinant clones of a λgt11 human skeletal muscle cDNA library (Clontech) were plated and screened following standard techniques (Sambrook et al., *supra*). The initial library screening was performed using the insert released from the clone 130347 that contains EST TIGR-A0044Z44, corresponding to the 3' end of the gene. Positive phages were plaque purified and phage DNA was isolated according to standard procedures (Sambrook et al., *supra*). The inserts of the positive clones were released by *EcoR*I digestion of phage DNA and subsequently subcloned into the *EcoR*I site of pBluescript II (KS+) vector (Stratagene).

Fifty cDNA clones were identified when a human skeletal muscle cDNA library was screened with the 130347 cDNA. Clone cDNA10 with the largest insert (~6.5 kb) (Fig. 1B) was digested independently with *BamH*I and *Pst*I and further subcloned into pBluescript vector. Miniprep DNA of cDNA clones and subclones of cDNA10 was prepared using the Qiagen plasmid Miniprep kit (Valencia, CA). Sequencing was carried out from both ends of each clone using the SequiTherm EXCEL™ long-read DNA sequencing kit (Epicenter, Madison, WI), fluorescent-labeled M13 forward and reverse primers, and a LI-COR sequencer (Lincoln, NE). Assembly of cDNA contigs and sequence analysis were performed using Sequencher software (Gene Codes Corporation, Inc., Ann Arbor, MI).

Two additional screens, first with the insert of cDNA10 and then a 683 bp PCR product (A27-F2R2) amplified from the 5′ end of the cDNA contig, identified 87 additional cDNA clones. Clones B22 and B33 extended the 5′ end by 94 and 20 bp, respectively. The compiled sequence allowed for the generation of a sequence of 6.9 kb (SEQ ID NO:1) (with 10-fold average coverage).

Although the 5′ end of the gene has not been further extended to the 8.5 kb predicted by Northern analysis, an open reading frame (ORF) of 6,243 bp has been identified within this 6.9 kb sequence. This ORF is preceded by an in-frame stop codon and begins with the sequence cgcaagc*ATG*CTG (SEQ ID NO:118); five of the first seven bp are consistent with the Kozak consensus sequence for a start codon (Kozak, 1989, *Nucl. Acids Res.* 15:8125-33; Kozak, 1989, *J. Cell. Biol.* 108:229-41). An alternate start codon, in the same frame, +75 bp downstream, appears less likely as a start site GAGACG*ATG*GGG (SEQ ID NO:119). Thus, the entire coding region of this candidate gene is believed to have been identified, as represented by the 6.9 kb sequence contig.

Isolation of the Brain-Specific Dysferlin Isoform

Identification of the brain-specific isoform of dysferlin

A brain-specific isoform of dysferlin was identified using Northern blot analysis of poly(A+)RNA derived from multiple human adult tissues probed with radiolabeled full-length dysferlin cDNA subclones. A prominent 7.2 kb transcript was detected on Northern blots in skeletal muscle, heart, placenta, lung, and kidney, while a distinct but equally prominent 3.6 kb-3.8 kb transcript was identified exclusively in the brain. Using long exposures, a faint 7.2 kb mRNA was also detected in the

brain. This finding suggested that the shorter brain isoform was likely to be a tissue-specific splice variant of the dysferlin gene. To test this hypothesis, a human brain cDNA library (Stratagene) was screened for the dysferlin brain isoform.

Cloning of the brain-specific dysferlin isoform

To identify probes that hybridize to the brain-specific dysferlin sequence and so could be used for library screening, fragments of the full-length dysferlin cDNA clone (derived from a skeletal muscle cDNA library) were generated using restriction enzymes. The fragments were about 1 kb in length and were analyzed by hybridization to a Northern blot that included brain RNA. Sequences suitable for library screening were those that hybridized to the 3.6-3.8 kb brain-specific transcript. A region of the 3' end of the dysferlin cDNA sequence that is approximately 3 kb in length was identified as hybridizing to brain mRNA. DNA containing sequence from this region was used as a probe for hybridization screening of a human brain cDNA library (Stratagene).

The human brain cDNA library was plated out and screened using standard procedures. Of the approximately 720,000 plaques screened, 63 primary positive clones were identified. Of these, 20 clones were selected for further analysis involving standard methods of hybridization, restriction enzyme mapping, and sequencing. The primary positive clones shared regions of overlap with each other.

Sequencing of positive clones, provided 3671 nucleotides of the brain-specific dysferlin sequence (SEQ ID NO:232; Figure 6A-B). The identified sequence corresponds closely to the size of the brain-specific dysferlin transcript detected on Northern blots. With the exception of the 5' region of the sequence, the

brain-specific sequence is identical to about 3.1 kb of the dysferlin sequence (from nucleotide 3722 to 6904 of the dysferlin sequence). In the dysferlin gene, position 3722 corresponds to the start of exon 32. This finding is consistent with the hypothesis that the brain isoform is a splice-variant of the dysferlin gene. At the 5' end of the brain isoform, 489 nucleotides are unique to brain-specific dysferlin. The amino acid sequence encoded by the brain dysferlin nucleic acid sequence (SEQ ID NO:233; Figure 6) contains a unique sequence with an initiation codon within a Kozak consensus sequence. The nucleic acid sequence unique to brain-specific dysferlin encodes a novel 24 amino acid sequence.

Identification of Mutations in Miyoshi Myopathy

Two strategies were used to determine whether this 6.9 kb cDNA (SEQ ID NO:1) is mutated in MM. First, the genomic organization of the corresponding gene was determined and the adjoining intronic sequence at each of the 55 exons which make up the cDNA was identified. To identify exon-intron boundaries within the gene, PAC DNA was extracted with the standard Qiagen -Mini Prep protocol. Direct sequencing was performed with DNA Sequence System (Promega, Madison, WI) using ^{32}P end-labeled primers (Benes et al., 1997, *Biotechniques* 23:98-100). Exon-intron boundaries were identified as the sites where genomic and cDNA sequences diverged. Second, in patients for whom muscle biopsies were available, RT-PCR was also used to prepare cDNA for the candidate gene from the muscle biopsy specimen.

Single strand conformational polymorphism analysis (SSCP) was used to screen each exon in patients from 12 MM families. Putative mutations identified in this way were confirmed by direct sequencing from genomic DNA using exon-specific intronic primers. Approximately 20

ng of total genomic DNA from immortalized lymphocyte cell lines were used as a template for PCR amplification analysis of each exon using primers (below) located in the adjacent introns. SSCP analysis was performed as previously described (Aoki et al., 1998, *Ann. Neurol.* 43:645-53). In patients for whom muscle biopsies were available, mRNA was isolated using RNA-STAT-60™ (Tel-Test, Friendswood, TX) and first-strand cDNA was synthesized from 1-2 μg total RNA with MMLV reverse transcriptase and random hexamer primers (Life Technologies, Gaithersburg, MD). Three μl of this product were used for PCR amplification. Eight sets of primers were designed for muscle cDNA, and overlapping cDNA fragments suitable for SSCP analysis were amplified. After initial denaturation at 94°C for 2 min, amplification was performed using 30 cycles at 94°C for 30 s, 56°C for 30 s, and 72°C for 60 s. The sequences of polymorphisms detected by SSCP analysis were determined by the dideoxy termination method using the Sequenase kit (US Biochemicals). In some instances, the base pair changes predicted corresponding changes in restriction enzyme recognition sites. Such alterations in restriction sites were verified by digesting the relevant PCR products with the appropriate restriction enzymes.

Primer pairs used for SSCP screening and exon sequencing are as follows:

(1) exon 3, F3261 5'-tctcttctcctagagggccatag-3' (SEQ ID NO: 101) and R326 5'-ctgttcctccccatcgtctcatgg-3' (SEQ ID NO: 102);

(2) exon 20, F3121 5'-gctcctcccgtgaccctctg-3' (SEQ ID NO: 103) and R3121 5'-gggtcccagccaggagcactg-3' (SEQ ID NO: 104);

(3) exon 36, F2102 5'-cccctctcaccatctcctgatgtg-3' (SEQ ID NO: 105) and R2111 5'-tggcttcaccttccctctacctcgg-3' (SEQ ID NO: 106);

(4) exon 49, F1081 5'-tcctttggtaggaaatctaggtgg-3' (SEQ ID NO: 107) and R1081 5'-ggaagctggacaggcaagagg-3' (SEQ ID NO: 108);

(5) exon 50, F1091 5'-atatactgtgttggaaatcttaatgag-3' (SEQ ID NO: 109) and R1091 5'-gctggcaccacagggaatcgg-3' (SEQ ID NO: 110);

(6) exon 51, F1101 5'-ctttgcttccttgcatccttctctg-3' (SEQ ID NO: 111) and R1101 5'-agcccccatgtgcagaatggg-3' (SEQ ID NO: 112);

(7) exon 52, F1111 5'-ggcagtgatcgagaaacccgg-3' (SEQ ID NO: 113) and R1111 5'-catgccctccactggggctgg-3' (SEQ ID NO: 114);

(8) exon 54, F1141 5'-ggatgcccagttgactccggg-3' (SEQ ID NO: 115) and R1141 5'-ccccaccacagtgtcgtcagg-3' (SEQ ID NO: 116);

(9) exon 29, F3031 5'-aagtgccaagcaatgagtgaccgg-3' (SEQ ID NO: 184) and R3021 5'-ctcactcccacccaccacctg-3' (SEQ ID NO: 185);

(10) exon 31, F2141 5'-gaatctgccataaccagcttcgtg-3' (SEQ ID NO: 188) and R2141 5'-tatcaccccatagaggcctcgaag-3' (SEQ ID NO: 189);

(11) exon 32, F2981 5'-cagccactcactctggcacctctg-3' (SEQ ID NO: 190) and R2981 5'-agcccacagtctctgactctcctg-3' (SEQ ID NO: 191);

(12) exon 43, F2031 5'-cagccaaaccatatcaacaatg-3' (SEQ ID NO: 210) and R2021 5'-ctggggaggtgagggctctag-3' (SEQ ID NO: 211);

(13) exon 44, F2011 5'-gaagtgttttgtctcctcctc-3' (SEQ ID NO: 212) and R2011 5'-gcaggcagccagcccccatc-3' (SEQ ID NO: 213);

(14) exon 46, F1041 5'-ctcgtctatgtcttgtgcttgctc-3' (SEQ ID NO: 216) and R1051 5'-caccatggtttggggtcatgtgg-3' (SEQ ID NO: 217).

These primers were used in SSCP screening and exon sequencing, and identified eighteen different mutations in fifteen families (Table 2).

Table 2

Mutations in Dysferlin in Distal Myopathy and LGMD[1]

Name	Nucleotide Change	Exon	Consequence	Origin	Family name	Allele	Change of restriction site
Mutations							
537insA	ins of A at 537	3	Frameshift	Arabic	MM59	Hom	no change
Q605X	CAG to TAG at 2186	20	Stop at 605	French	MM67	Hom	-Pst I, -Fnu 4H I[1]
I1298V	ATC to GTC at 4265	36	Amino acid change	Italian	MM, LGMD56	Het	-BamHI, -BStYI; +Ava II
E1883X	GAG to TAG at 5870	49	Stop at 1883	English	MM8	Het	no change
H1857R	CAT to CGT at 5943	50	Amino acid change	English	MM50	Het	no change

	5966delG	del of G at 5966	50	Frameshift	Spanish	DMAT71	Hom	no change
	5966delG	del of G at 5966	50	Frameshift	Spanish	MM75	Hom	no change
	6071/6072delAG	del of AG at 6071/6072	51	Frameshift	English	MM58	Het	no change
	6319+1G to A	Ggt to Gat at 6319+1	52	5' splice site	English	MM8	Het	no change
	R2042C	CGT to TGT at 6497	54	Amino acid change	Italian	MM56	Het	-Fnu4HI
	R1046H	CGC to CAG at 3510	29	Amino acid change	Japanese	MM10	Hom	-HinPI, -Fsp I
	3746delG	del of G at 3746	31	Frameshift	Japanese	MM17	Hom	-MboII
	Q1160X	CAG to TAG at 3851	32	Stop at 1160	Mexican	MM46	Hom	-ScrFI, -BstNI, +MaeI, +BfaI

	5122/5123delCA	del of CA at 5122/5123, A to T at 5121	43	Frameshift	Japanese	MM14	Het	no change
	R1586X	CGA to TGA at 5129	43	Stop at 1586	Japanese	MM12	Hom	+Dde I
	5245delG	del of G at 5245 and G to C at 5249, or G to C at 5245 and del G at 5249	44	Frameshift	French	MM63	Hom	-Bpm I, -BanII + AvaII, +Sau96I
5	E1732X	GAG to TAG at 5567	46	Stop at 1732	Spanish	MM73	Het	-Mbo II
	2573-77 Hom del ACCCA	Del of ACCCA at 2573-77 ?Please provide	23	Frameshift	Italian	MM69		

[1] MM: Miyoshi myopathy; DMAT: distal myopathy with anterior tibial onset; LGMD: limb girdle muscular dystrophy

[2] +: create a new restriction site, -: eliminate an existing restriction site.

Twelve of the eighteen different mutations are predicted to block dysferlin expression, either through nonsense or frameshift changes. Seven of the thirteen samples are homozygous and thus expected to result in complete loss of dysferlin function. For each mutated exon in these patients, at least 50 control DNA samples (100 chromosomes) were screened to determine the frequencies of the sequence variants. When possible, the parents and siblings of affected individuals were also screened to verify that defined mutations were appropriately co-inherited with the disease in each pedigree (Fig. 4). In two families (50, 58 in Table 2) heterozygous mutations were identified in one allele (respectively a missense mutation and a 2 bp deletion). Mutations in the other allele are presumed to have not been detected (or in three of the screened MM families) either because the mutant and normal SSCP products are indistinguishable or because the mutation lies outside of coding sequence (i.e., in the promoter or a regulatory region of an intron). The disease-associated mutations did not appear to arise in the population as common polymorphisms.

More mutations can be identified by using appropriate primer pairs to amplify an exon and analyze its sequence. The following primer pairs are useful for exon amplification.

Exon	Code	Primer Sequence
1	F408	5'-gacccacaagcggcgcctcgg-3'{SEQ ID NO: 130}
	F4101	5'-gaccccggcgagggtggtcgg-3'{SEQ ID NO: 131}
2	F4111	5'-tgtctctccattctccctttgtg-3'{SEQ ID NO:132}
	R4111	5''-aggacactgctgagaaggcacctc-3'{SEQ ID NO: 133}

	3	F3262	5-agtgccctggtggcacgaagg-3' {SEQ ID NO: 134}
		R3261	5-cctacctgcaccttcaagccatgg-3' {SEQ ID NO: 135}
	4	F3251	5-cagaagagccagggtgccttagg-3' {SEQ ID NO: 136}
		R3251	5-ccttggaccttaacctggcagagg-3' {SEQ ID NO: 137}
	5	F3242	5-cgaggccagcgcaccaacctg-3' {SEQ ID NO: 138}
		R3242	5-actgccggccattcttgctggg-3' {SEQ ID NO: 139}
	6	F3231	5-ccaggcctcattagggccctc-3' {SEQ ID NO: 140}
		R3231	5-ctgaagaggagcctggggtcag-3' {SEQ ID NO: 141}
	7	F3222	5-ctgagatttctgactcttggggtg-3' {SEQ ID NO: 142}
		R3211	5-aaggttctgccctcatgccccatg-3' {SEQ ID NO: 143}
	8	F3561	5-ctggcctgagggatcagcagg-3' {SEQ ID NO: 144}
		R3561	5-gtgcatacatacagcccacggag-3' {SEQ ID NO: 145}
	9	F3551	5-gagctattgggttggccgtgtggg-3' {SEQ ID NO: 146}
		R3552	5-accaacacggagaagtgagaactg-3' {SEQ ID NO: 147}
	10	F3201	5-ccacactttatttaacgctttggcgg-3'{SEQ ID NO: 148}
		R3201	5-cagaaccaaaatgcaaggatacgg-3' {SEQ ID NO: 149}
	11	F3191	5-cttctgattctgggatcaccaaagg-3' {SEQ ID NO: 150}

F3191 5-ggaccgtaaggaagacccaggg-3' {SEQ ID NO: 151}

12 F3181 5-cctgtgctcaggagcgcatgaagg-3'{SEQ ID NO: 152}

R3181 5-gcagacctcccacccaagggcg-3' {SEQ ID NO: 153}

13 F3171 5-gagacagatgggggacagtcaggg-3' {SEQ ID NO: 154}

R3171 5-cctcccgagagaaccctcctg-3' {SEQ ID NO: 155}

14 F3161 5-gggagcccagagtccccatgg-3' {SEQ ID NO: 156}

R3161 5-gggcctccttgggtttgctgg-3' {SEQ ID NO: 157}

15 F3541 5-gcctccccagcatcctgccgg-3' {SEQ ID NO: 158}

R3541 5-tcactgagccgaatgaaactgagg-3' {SEQ ID NO: 159}

16 F3531 5-tgtggcctgagttcctttcctgtg-3' {SEQ ID NO: 160}

R3531 5-ggtcaaagggcagaacgaagaggg-3' {SEQ ID NO: 161}

17 F3151 5-cccgtccttctcccagccatg-3' {SEQ ID NO: 162}

R3151 5-ctcccctggttgtccccaagg-3' {SEQ ID NO: 163}

18 F3141 5-cgacccctctgattgccacttgtg-3' {SEQ ID NO: 164}

R3141 5-ggcatcctgcccttgccaggg-3' {SEQ ID NO: 165}

19 F3522 5-tctgtctcccctgctccttg-3' {SEQ ID NO: 166}

R3522 5-cttccctgccccgacgcccag-3' {SEQ ID NO: 167}

20 F3121 5-gctcctcccgtgaccctctgg-3' {SEQ ID NO: 103}
R3121 5-gggtcccagccaggagcactg-3' {SEQ ID NO: 104}
21 F3111 5-cagcgctcaggcccgtctctc-3' {SEQ ID NO: 168}
R3111 5-tgcataggcatgtgcagctttggg-3' {SEQ ID NO: 169}
22 F3512 5-catgcaccctctgccctgtgg-3' {SEQ ID NO: 170}
R3512 5-agttgagccaggagaggtggg-3' {SEQ ID NO: 171}
23 F3101 5-catcaggcgcattccatctgtccg-3' {SEQ ID NO: 172}
R3091 5-agcaggagagcagaagaagaaagg-3' {SEQ ID NO: 173}
24 F3082 5-gtgtgtcaccatccccaccccg-3' {SEQ ID NO: 174}
R3082 5-caagagatgggagaaaggccttatg-3' {SEQ ID NO:175}
25 F3073 5-ctgggacatccggatcctgaagg-3' {SEQ ID NO: 176}
R3073 5-tccaggtagtgggaggcagagg-3' {SEQ ID NO: 177}
26 F3061 5-tcccactacctggagctgccttgg-3' {SEQ ID NO: 178}
R3051 5-ggctctccccagccctccctg-3' {SEQ ID NO: 179}
27 F3601 5-cagagcagcagagactctgaccag-3' {SEQ ID NO: 180}
R3601 5-tagaccccacctgcccctgag-3' {SEQ ID NO: 181}
28 F3501 5-tcctctcattgcttgcctgttcgg-3' {SEQ ID NO: 182}

R3501 5-ttgagagcttgccggggatgg-3' {SEQ ID NO: 183}

29 F3031 5-aagtgccaagcaatgagtgaccgg-3' {SEQ ID NO: 184}

R3021 5-ctcactcccacccaccacctg-3' {SEQ ID NO: 185}

30 F3011 5-cccaccggcctctgagtctgc-3' {SEQ ID NO: 186}

R3001 5-accctacccaagccaggacaagtg-3' {SEQ ID NO: 187}

31 F2141 5-gaatctgccataaccagcttcgtg-3' {SEQ ID NO: 188}

R2141 5-tatcaccccatagaggcctcgaag-3' {SEQ ID NO: 189}

32 F2981 5-cagccactcactctggcacctctg-3' {SEQ ID NO: 190}

R2981 5-agcccacagtctctgactctcctg-3' {SEQ ID NO: 191}

33 F2131 5-acatctctcagggtccctgctgtg-3' {SEQ ID NO: 192}

R2211 5-cctgtgaggggacgaggcagg-3' {SEQ ID NO: 193}

34 F2202 5-gccctgggtaagggatgctgattc-3' {SEQ ID NO: 194}

R2202 5-cctgcctgggcctcctggatc-3' {SEQ ID NO: 195}

35 F2111 5-gagggtgatgggggccttagg-3' {SEQ ID NO: 196}

R2112 5-gcaatcagtttgaagaaggaaagg-3' {SEQ ID NO: 197}

36 F2102 5-cccctctcaccatctcctgatgtg-3' {SEQ ID NO: 105}

R2111 5-ggcttcaccttccctctacctcgg-3' {SEQ ID NO: 106}

37 F2101 5-caccttgtctccattctacctgc-3' {SEQ ID NO: 198}
R2101 5-ctcccagcccccacgcccagg-3' {SEQ ID NO: 199}
38 F2091 5-ctgagccactctcctcattctgtg-3' {SEQ ID NO: 200}
R2091 5-tggaaggggacagtagggagg-3' {SEQ ID NO: 201}
39 F2081 5-ggccagtgcgttcttcctcctc-3' {SEQ ID NO: 202}
R2071 5-tccctgacctgcccatcatctc-3' {SEQ ID NO: 203}
40 F2061 5-gcccctgtcaggcctggatgg-3' {SEQ ID NO: 204}
R2061 5-tgacccaggcctccctggagg-3' {SEQ ID NO: 205}
41 F2051 5-ctgaaatggtctctttctttctac-3' {SEQ ID NO: 206}
R2051 5-cacaccgactgtcagactgaagag-3' {SEQ ID NO: 207}
42 F2041 5-ttgtcccctcctctaatccccatg-3' {SEQ ID NO: 208}
R2041 5-gggttagggacgtcttcgagg-3' {SEQ ID NO: 209}
43 F2031 5-cagccaaaccatatcaacaatg-3' {SEQ ID NO: 210}
R2021 5-ctggggaggtgagggctctag-3' {SEQ ID NO: 211}
44 F2011 5-gaagtgttttgtctcctcctc-3' {SEQ ID NO: 212}
R2011 5-gcaggcagccagcccccatc-3' {SEQ ID NO: 213}
45 F1021 5-gggtgccctgtgttggctgac-3' {SEQ ID NO: 214}

R1031 5-gcaggcagccagcccccatc-3' {SEQ ID NO: 215}

46 F1041 5-ctcgtctatgtcttgtgcttgctc-3' {SEQ ID NO: 216}

R1051 5-caccatggtttggggtcatgtgg-3' {SEQ ID NO: 217}

47 F1061 5-tctcgcttccccagctcctgc-3' {SEQ ID NO: 218}

R1061 5-tctggagttcgaggactctggg-3' {SEQ ID NO: 219}

48 F1071 5-agaagggtggggagagaacgg-3' {SEQ ID NO: 220}

R1071 5-cagctcagagcctgtggctgg-3' {SEQ ID NO: 221}

49 F1082 5-aaggccttcccatcctttggtagg-3' {SEQ ID NO: 222}

R1082 5-acaacccagagggagcacggg-3' {SEQ ID NO: 223}

50 F1092 5-gttgacgatgtatatactgtgttgg-3' {SEQ ID N0: 224}

R1091 5-gctggcaccacagggaatcgg-3' {SEQ ID NO: 110}

51 F1102 5-gcctctctctaactttgcttccttg-3' {SEQ ID NO: 225}

R1101 5-agcccccatgtgcagaatggg-3' {SEQ ID NO: 112}

52 F1112 5-ggctacaggctggcagtgatcgag-3' {SEQ ID NO: 226}

R1112 5-ttcccccatgccctccactgg-3' {SEQ ID NO: 227}

53 F1121 5-agccttcgtgcccctaaccaagtg-3' {SEQ ID NO: 228}

R1121 5-ctgtgggcattggggctcagg-3' {SEQ ID NO: 229}

54	F1141	5-ggatgcccagttgactccggg-3'	{SEQ ID NO: 115}
	R1141	5-ccccaccacagtgtcgtcagg-3'	{SEQ ID NO: 116}
55	F1151	5-gccccagtgggatcaccatg-3'	{SEQ ID NO: 230}
	R116	5-atgctggaggggaccccacgg-3'	{SEQ ID NO: 231}

Comparison of Dysferlin With Other Proteins

The 6,243 bp ORF of this candidate MM gene is predicted to encode 2,080 amino acids (Figs. 1C and 2; SEQ ID NO:2). At the amino acid level, this protein is highly homologous to the nematode (*Caenorhabditis elegans*) protein fer-1 (27% identical, 57% identical or similar: the sequence alignment and comparison was performed using http://vega.igh.cnrs.fr/bin/nph-align_query.pl.) (Argon & Ward, 1980, *Genetics* 96:413-33; Achanzar & Ward, 1997, *J. Cell Science* 110:1073-81). This *dys*trophy-associated, *fer*-1-*like* protein has therefore been designated "dysferlin."

The fer-1 protein was originally identified through molecular genetic analysis of a class of fertilization-defective *C. elegans* mutants in which spermatogenesis is abnormal (Argon & Ward, 1980, *Genetics* 96:413-33). The mutant fer-1 spermatozoa have defective mobility and show imperfect fusion of membranous organelles (Ward et al., 1981, *J. Cell Bio.* 91:26-44). Like fer-1, dysferlin is a large protein with an extensive, highly charged hydrophilic region and a single predicted membrane spanning region at the carboxy terminus (Fig. 3). There is a membrane retention sequence 3' to the membrane spanning stretch, indicating that the protein may be preferentially targeted to either endoplasmic or sarcoplasmic reticulum, probably as a Type II protein

(i.e. with the NH_2 end and most of the following protein located within the cytoplasm) (Fig. 1C). Several nuclear membrane targeting sequences are predicted within the cytoplasmic domain of the protein (http://psort.nibb.ac.jp/form.html). Immunocytochemical detection of dysferlin suggests that dysferlin is targeted to or anchored within the sarcoplasmic reticulum.

The cytoplasmic component of this protein contains four motifs homologous to C2 domains. C2 domains are intracellular protein modules composed of 80 - 130 amino acids (Rizo & Sudhof, 1998, *J. Biol. Chem.* 273:15897). Originally identified within a calcium-dependent isoform of protein kinase C (Nishizuka, 1988, *Nature* 334:661-65), C2 domains are present in numerous proteins. These domains often arise in approximately homologous pairs described as double C2 or DOC2 domains. One DOC2 protein, DOC2α, is brain specific and highly concentrated in synaptic vesicles (Orita et al., 1995, *Biochem. Biophys. Res. Comm.* 206:439-48), while another, DOC2β, is ubiquitously expressed (Sakaguchi et al., 1995, *Biochem. Biophys. Res. Comm.* 217:1053-61). Many C2 modules can fold to bind calcium, thereby initiating signaling events such as phospholipid binding. At distal nerve terminals, for example, the synaptic vesicle protein synaptotagmin has two C2 domains that, upon binding calcium, permit this protein to interact with syntaxin, triggering vesicle fusion with the distal membrane and neurotransmitter release (Sudhof & Rizo, 1996, *Neuron* 17:379-88).

The four dysferlin C2 domains are located at amino acid positions 32-82, 431-475, 1160-1241, and 1582-1660 (Figs. 1C and 3). Indeed, it is almost exclusively through these regions that dysferlin has homology to any proteins other than fer-1. Each of these segments in

dysferlin is considerably smaller than a typical C2 domain. Moreover, these segments are more widely separated in comparison with the paired C2 regions in synaptotagmin, DOC2α and β and related C2-positive proteins. For this reason, it is difficult to predict whether the four relatively short C2 domains in dysferlin function analogously to conventional C2 modules. That dysferlin might, by analogy with synaptotagmin, signal events such as membrane fusion is suggested by the fact that fer-1 deficient worms show defective membrane organelle fusion within spermatozoa (Ward et al., 1981, *J. Cell Bio.* 91:26-44).

The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

EXAMPLES

Example 1: Production of dysferlin protein

Standard methods can be used to synthesize either wild type or mutant dysferlin, or fragments of either. These methods can also be used to synthesize brain-specific dysferlin polypeptides including full-length or fragments (e.g., a polypeptide unique to brain-specific dysferlin). For example, a recombinant expression vector encoding dysferlin (or a fragment thereof: e.g., dysferlin minus its membrane-spanning region) operably linked to appropriate expression control sequences can be used to express dysferlin in a prokaryotic (e.g., E.coli) or eukaryotic host (e.g., insect cells, yeast cells, or mammalian cells). The protein is then purified by standard techniques. If desired, DNA encoding part or all of the dysferlin sequence can be joined in-frame to DNA encoding a different polypeptide, to produce a chimeric DNA that encodes a hybrid polypeptide. This can be used, for example, to add a tag that will simplify identification or purification of the expressed protein,

or to render the dysferlin (or fragment thereof) more immunogenic.

The preferred means for making short peptide fragments of dysferlin is by chemical synthesis. These fragments, like dysferlin itself, can be used to generate antibodies, or as positive controls for antibody-based assays.

Fusion proteins are useful, e.g., for generating antibodies. Such fusion proteins are generated using known methods. In one example, to construct glutathione S-transferase (GST):dysferlin fusion proteins, the BLAST program (Altschul et al., 1990, J. Molec. Biol. 215:403-410) was used to identify three regions of the dysferlin cDNA that show no homology to any known human proteins (Figure 1). These were subcloned from the dysferlin cDNA as BstYI (881-1333), XmnI (1990-2718) and SalI (5364-5732) fragments ligated respectively into BamHI, SmaI and SalI sites of pGEX-5X-3 (Pharmacia). The three fragments correspond to amino acid sequences at amino acid locations 253-403, 624-865, and 1664-1786 of SEQ ID NO:2, respectively. The resulting GST fusion proteins of BamHI (43 kDa) and SmaI (53.3 kDa) formed isoluble aggregates that were isolated by SDS-PAGE. The fusion protein of SalI (40.2 kDa) was soluble and thus could be purified using a glutathione Sepharose 4B column; the SalI dysferlin fragment (14.2 kDa) was isolated by cleavage from GST using Factor Xa protease. The eluted protein was concentrated and further purified by SDS-PAGE. For all three of the fusion peptides, the resulting SDS-PAGE bands were excised and used to immunize rabbits.

Example 2: Production and characterization of anti-dysferlin antibodies

Techniques for generating both monoclonal and polyclonal antibodies specific for a particular protein

are well known. The antibodies can be raised against a short peptide epitope of dysferlin, an epitope linked to a known immunogen to enhance immunogenicity, a long fragment of dysferlin, or the intact protein. Antibodies can also be raised against brain-specific dysferlin polypeptides, e.g., against amino acids 1-24 of SEQ ID NO:233. Such antibodies raised against dysferlin or brain-specific dysferlin polypeptides are useful for e.g., localizing such polypeptides in tissue sections or fractionated cell preparations and diagnosing dysferlin-related disorders.

An isolated dysferlin protein, or a portion or fragment thereof, can be used as an immunogen to generate antibodies that bind dysferlin using standard techniques for polyclonal and monoclonal antibody preparation. The dysferlin immunogen can also be a mutant dysferlin or a fragment of a mutant dysferlin. A full-length dysferlin protein can be used or, alternatively, antigenic peptide fragments of dysferlin can be used as immunogens. The antigenic peptide of dysferlin comprises at least 8 (preferably 10, 15, 20, or 30) amino acid residues of the amino acid sequence shown in SEQ ID NO:2 and encompasses an epitope of such that an antibody raised against the peptide forms a specific immune complex with dysferlin. Preferred epitopes encompassed by the antigenic peptide are regions of dysferlin that are located on the surface of the protein, e.g., hydrophilic regions.

A dysferlin immunogen typically is used to prepare antibodies by immunizing a suitable subject (e.g., rabbit, goat, mouse or other mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed dysferlin protein or a chemically synthesized dysferlin polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar

immunostimulatory agent. Immunization of a suitable subject with an immunogenic dysferlin preparation induces a polyclonal anti-dysferlin antibody response.

Polyclonal anti-dysferlin antibodies ("dysferlin antibodies") can be prepared as described above by immunizing a suitable subject with a dysferlin immunogen. The dysferlin antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized dysferlin. If desired, the antibody molecules directed against dysferlin can be isolated from the mammal (e.g., from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, e.g., when the dysferlin antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell hybridoma technique (Kozbor et al. (1983) *Immunol. Today* 4:72), the EBV-hybridoma technique (Cole et al. (1985), *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing hybridomas is well known (*see generally Current Protocols in Immunology* (1994) Coligan et al. (eds.) John Wiley & Sons, Inc., New York, NY). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with a dysferlin immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds dysferlin.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied

for the purpose of generating a monoclonal antibody against dysferlin (*see, e.g., Current Protocols in Immunology, supra*; Galfre et al. (1977) *Nature* 266:55052; R.H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); and Lerner (1981) *Yale J. Biol. Med.*, 54:387-402. Moreover, the one in the art will appreciate that there are many variations of such methods which also would be useful. Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind dysferlin, e.g., using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal dysferlin antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with dysferlin to thereby isolate immunoglobulin library members that bind dysferlin. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse et al. (1989) *Science*

246:1275-1281; Griffiths et al. (1993) *EMBO J.* 12:725-734.

As an example, two polyclonal antisera were raised for each of the fusion peptide antigens described above using New Zealand White rabbits. The rabbits were injected with 0.5 mg of antigen using keyhole limpet hemocyanin (KLH) as the adjuvent. Booster injections of 0.25 mg antigen were administered every three weeks over 12 weeks. Serum was prepared from the rabbits and was purified using affinity column chromatography (HiTrap; Pharmacia) or antigen-blotted polyvinylidene difluoride (PVDF) membrane.

Immunoblotting was used to verify that the affinity-purified antisera recognize the cognate fusion peptides by Western immunoblotting (WIB) and that this reactivity was immunoadsorbed by pre-incubation of the antisera with the peptides. Thus, antiserum raised against the polypeptide encoded by the SalI fragment (encoding amino acids 1664-1786) identified the fragment both as a cleaved, 14.2 kDa fragment and as a component of the 40.2 kDa GST-SalI fusion peptide. No reactivity was evident in the fraction containing only the GST fusion partner. Immunoadsorption entirely abolished this staining. Analogous results were detected with all six antisera (to the three different target fusion peptides).

Preparation of subcellular fractions

Frozen human muscle (0.3 g) was homogenized in five volumes of 0.25 M sucrose containing proteinase inhibitor (Complete, Boehringer). Subcellular fractions of nuclei, mitochondria, microsomes, and cytosol were separated by differential centrifugation. The purity of each fraction was evaluated by immunoblotting of fraction-specific proteins with antibodies to histone H1 (Calbiochem), cytochrome c (Santa Cruz), Na^+-K^+ ATPase α1 subunit

(Research Diagnostics) and cytosolic superoxide dismutase (Calbiochem).

Dysferlin in subcellular fractions

Immunoblotting was used to analyze dysferlin expression. Twenty μg of each subcellular fraction and 40 μg of whole homogenate of muscle were separated by SDS-PAGE (4-15% gradient gel) and transferred to a nitrocellulose membrane. Immunoblotting was performed according to standard methods, using chemiluminescence (ECL, Amersham). Immunoblotting of multi-tissue blots identified prominent dysferlin positively at approximately 230 kDa in heart, placenta, skeletal muscle and kidney. Little or no immuno-positive staining was detected in brain, liver, spleen, ovary, or testis. Lower molecular weight bands (approximately 40 kDa) were also evident. Immunoadsorption with the corresponding fusion peptide abolished both the large and the smaller bands. The 230 kDa band was observed with all of the affinity purified, anti-dysferlin antisera.

Immunoblotting of fractionated human muscle documented distinct 230 kDa bands in the whole muscle homogenate an in microsomal and nuclear fractions. Some immunoreactivity was also evident in the nuclear and mitochondrial fractions. No immunoreactivity was detected in the cytosolic fractions. This pattern was seen with all of the anti-dysferlin antisera, and was eliminated by immunoadsorption. The identity of the assayed fractions was verified by Western blotting using fraction-specific antibodies: histone HI for the nuclear fraction, cytochrome c for the mitochondrial fraction, Na^+-K^+ ATPase α1-subunit for the microsomal fraction, and SOD1 for the cytosolic fraction.

Example 3: Diagnosis

The discovery of mutations in the dysferlin gene that are associated with the MM and LMGD2B phenotypes means that individuals can be tested for the disease gene before symptoms appear. This will permit genetic testing and counseling of those with a family history of the disease. Additionally, individuals diagnosed with the genetic defect can be closely monitored for the appearance of symptoms, thereby permitting early intervention, including genetic therapy, as appropriate. Individuals with a brain-specific dysferlin-related disorder can be diagnosed using such methods.

Diagnosis can be carried out on any suitable genomic DNA sample from the individual to be tested. Typically, a blood sample from an adult or child, or a sample of placental or umbilical cord cells of a newborn would be used; alternatively, one could utilize a fetal sample obtained by amniocentesis or chorionic villi sampling.

It is expected that standard genetic diagnostic methods can be used. For example, PCR can be utilized to identify the presence of a deletion, addition, or substitution of one or more nucleotides within any one of the exons of dysferlin. Following the PCR reaction, the PCR product can be analyzed by methods such as a heteroduplex detection technique based upon that of White et al. (1992, *Genomics* 12:301-06), or by techniques such as cleavage of RNA-DNA hybrids using RNase A (Myers et al., 1985, *Science* 230:1242-46), single-stranded conformation polymorphism (SSCP) analysis (Orita et al., 1989, *Genomics* 10:298-99), di-deoxy-fingerprinting (DDF) (Blaszyk et al., 1995, *Biotechniques* 18: 256-260) and denaturing gradient gel electrophoresis (DGGE; Myers et al., 1987, *Methods Enzymol.* 155:501-27). The PCR may be carried out using a primer which adds a G+C rich sequence (termed a "GC-clamp") to one end of the PCR product, thus improving the sensitivity of the subsequent DGGE

procedure (Sheffield et al., 1989, *Proc. Natl. Acad. Sci. USA* 86:232-36). If the particular mutation present in the patient's family is known to have removed or added a restriction site, or to have significantly increased or decreased the length of a particular restriction fragment, a protocol based upon restriction fragment length polymorphism (RFLP) analysis (perhaps combined with PCR) may be appropriate.

The apparent genetic heterogeneity resulting in the MM/LGMD2B phenotypes means that the nature of the particular mutation carried by affected individuals in the patient's family may have to be ascertained prior to attempting genetic diagnosis of the patient. Alternatively, a battery of tests designed to identify any of several mutations known to result in MM/LGMD2B may be utilized to screen individuals without a defined familial genotype. The analysis can be carried out on any genomic DNA derived from the patient, typically from a blood sample.

Instead of basing the diagnosis on analysis of the genomic DNA of a patient, one could seek evidence of the mutation in the level or nature of the relevant expression products. Well-known techniques for analyzing expression include mRNA-based methods, such as Northern blots and *in situ* hybridization (using a nucleic acid probe derived from the relevant cDNA), and quantitative PCR (as described in St-Jacques et al., 1994, *Endocrinology* 134:2645-57). One could also employ polypeptide based methods, including the use of antibodies specific for the polypeptide of interest. These techniques permit quantitation of the amount of expression of a given gene in the tissue of interest, at least relative to positive and negative controls. One would expect an individual who is heterozygous for a genetic defect affecting the level of expression of

dysferlin to show up to a 50% loss of expression of this gene in such a hybridization or antibody-based assay. An antibody specific for the carboxy terminal end would be likely to pick up (by failure to bind to) most or all frameshift and premature termination signal mutations, as well as deletions of the carboxy terminal sequence. Use of a battery of monoclonal antibodies specific for different epitopes of dysferlin would be useful for rapidly screening cells to detect those expressing mutant forms of dysferlin (i.e., cells which bind to some dysferlin-specific monoclonal antibodies, but not to others), or for quantifying the level of dysferlin on the surface of cells. One could also use a protein truncation assay (Heim et al., 1994, *Nature Genetics* 8:218-19) to screen for any genetic defect which results in the production of a truncated polypeptide instead of the wild type protein.

Use of immunodetection to identify normal and disease-associated dysferlin

In the following example, immunodetection methods are used to demonstrate a detectable difference in muscles homogenates between normal and disease-associated dysferlin alleles.

Frozen muscle samples (quadriceps) were homogenized in ten volumes of SDS-PAGE sample buffer and boiled for 5 minutes. The final loading volume of SDS-PAGE was adjusted after densitometric measurements (NIH Image) of myosin heavy chain on the Coomassie blue stained gels. Studies were performed on six MM, two LGMD-2B, and three normal muscle samples.

Immunocytochemistry was performed on 8 micron cryostat sections of the muscle that were fixed in 100% cold acetone for 5 minutes and preincubated with PBS containing 1% BSA, 5% heat-inactivated goat serum and 0.2% Triton®X-100. The sections were incubated with

primary antibodies overnight at 4°C and fluorescein-labeled secondary (TAGO Immunologicals) for 30 minutes at room temperature. The primary antibodies were applied in two double staining combinations: SalI-1 anti-dysferlin and anti-dystrophin antibodies, and SalI-2 anti-dysferlin and anti-δ-sarcoglycan antibodies. The sections were mounted in SlowFade (Molecular Probes).

The 230 kDA antigen was absent in samples from all five MM patient in immunoblot assays. All five patients had normal patterns of dystrophin expression. Genetic analysis of the dysferlin gene in the patients predicted that at least two of the five MM patients should have no full-length protein. Two of the other three patients had mutations in at least one allele that are predicted to eliminate normal dysferlin expression. In all five patients, absence of dysferlin immuno-staining was documented with at least two other anti-dysferlin anti-sera.

Immunostaining of dysferlin, dystrophin and δ-sarcoglycan proteins demonstrated distinct membrane-associated positivity for each protein in normal muscle. By contrast, in both MM and LGMD-2B muscle the dysferlin protein was absent, while the dystrophin and δ-sarcoglycan proteins appeared normal.

Therapeutic Treatment

A patient with MM/LGMD2B, or an individual genetically susceptible to contracting one or both of these diseases, can be treated by supplying dysferlin therapeutic agents of the present invention. Dysferlin therapeutic agents include a DNA or a subgenomic polynucleotide coding for a functional dysferlin protein. A DNA (e.g., a cDNA) is prepared which encodes the wild type form of the gene operably linked to expression control elements (e.g., promoter and enhancer) that

induce expression in skeletal muscle cells or any other affected cells. The DNA may be incorporated into a vector appropriate for transforming the cells, such as a retrovirus, adenovirus, or adeno-associated virus. One of the many other known types of techniques for introducing DNA into cells *in vivo* may be used (e.g., liposomes). Particularly useful would be naked DNA techniques, since naked DNA is known to be readily taken up by skeletal muscle cells upon injection into muscle. Wildtype dysferlin protein can also be administered to an individual who either expresses mutant dysferlin protein or expresses an inadequate amount of dysferlin protein, *e.g.*, a MM/LGMD2B patient.

Administration of the dysferlin therapeutic agents of the invention can include local or systemic administration, including injection, oral administration, particle gun, or catheterized administration, and topical administration. Various methods can be used to administer the therapeutic dysferlin composition directly to a specific site in the body. For example, a specific muscle can be located and the therapeutic dysferlin composition injected several times in several different locations within the body of the muscle. The therapeutic dysferlin composition can be directly administered to the surface of the muscle, for example, by topical application of the composition. X-ray imaging can be used to assist in certain of the above delivery methods. Combination therapeutic agents, including a dysferlin protein or polypeptide or a subgenomic dysferlin polynucleotide and other therapeutic agents, can be administered simultaneously or sequentially.

Receptor-mediated targeted delivery of therapeutic compositions containing dysferlin subgenomic polynucleotides to specific tissues can also be used. Receptor-mediated DNA delivery techniques are described

in, for example, Findeis et al. (1993), *Trends in Biotechnol. 11*, 202-05; Chiou et al. (1994), Gene Therapeutics: Methods and Applications of Direct Gene Transfer (J.A. Wolff, ed.); Wu & Wu (1988), *J. Biol. Chem. 263*, 621-24; Wu et al. (1994), *J. Biol. Chem. 269*, 542-46; Zenke et al. (1990), *Proc. Natl. Acad. Sci. U.S.A. 87*, 3655-59; Wu et al. (1991), *J. Biol. Chem. 266*, 338-42.

Alternatively, a dysferlin therapeutic composition can be introduced into human cells *ex vivo*, and the cells then implanted into the human. Cells can be removed from a variety of locations including, for example, from a selected muscle. The removed cells can then be contacted with the dysferlin therapeutic composition utilizing any of the above-described techniques, followed by the return of the cells to the human, preferably to or within the vicinity of a muscle. The above-described methods can additionally comprise the steps of depleting fibroblasts or other contaminating non-muscle cells subsequent to removing muscle cells from a human.

Both the dose of the dysferlin composition and the means of administration can be determined based on the specific qualities of the therapeutic composition, the condition, age, and weight of the patient, the progression of the disease, and other relevant factors. If the composition contains dysferlin protein or polypeptide, effective dosages of the composition are in the range of about 1 μg to about 100 mg/kg of patient body weight, e.g., about 50 μg to about 50 mg/kg of patient body weight, e.g., about 500 μg to about 5 mg/kg of patient body weight.

Therapeutic compositions containing dysferlin subgenomic polynucleotides can be administered in a range of about 0.1 μg to about 10 mg of DNA/dose for local administration in a gene therapy protocol. Concentration

ranges of about 0.1 μg to about 10 mg, e.g., about 1 μg to about 1 mg, e.g., about 10 μg to about 100 μg of DNA can also be used during a gene therapy protocol. Factors such as method of action and efficacy of transformation and expression are considerations that will effect the dosage required for ultimate efficacy of the dysferlin subgenomic polynucleotides. Where greater expression is desired over a larger area of tissue, larger amounts of dysferlin subgenomic polynucleotides or the same amounts readministered in a successive protocol of administrations, or several administrations to different adjacent or close tissue portions of for example, a muscle site, may be required to effect a positive therapeutic outcome. In all cases, routine experimentation in clinical trials will determine specific ranges for optimal therapeutic effect.

Animal Model

A line of transgenic animals (e.g., mice, rats, guinea pigs, hamsters, rabbits, or other mammals) can be produced bearing a transgene encoding a defective form of dysferlin. Standard methods of generating such transgenic animals would be used, e.g., as described below.

Alternatively, standard methods of producing null (i.e., knockout) mice could be used to generate a mouse which bears one defective and one wild type allele encoding dysferlin. If desired, two such heterozygous mice could be crossed to produce offspring which are homozygous for the mutant allele. The homozygous mutant offspring would be expected to have a phenotype comparable to the human MM and/or LGMD2B phenotype, and so serve as models for the human disease.

For example, in one embodiment, dysferlin mutations are introduced into a dysferlin gene of a cell, e.g., a

fertilized oocyte or an embryonic stem cell. Such cells can then be used to create non-human transgenic animals in which exogenous altered (e.g., mutated) dysferlin sequences have been introduced into their genome or homologously recombinant animals in which endogenous dysferlin nucleic acid sequences have been altered. Such animals are useful for studying the function and/or activity of dysferlin and for identifying and/or evaluating modulators of dysferlin function. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologously recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous dysferlin gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, e.g., an embryonic cell of the animal, prior to completed development of the animal.

A transgenic animal of the invention can be created by introducing a nucleic acid encoding a dysferlin mutation into the male pronuclei of a fertilized oocyte, e.g., by microinjection or retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. A dysferlin cDNA sequence e.g., that of (SEQ ID NO:1 or SEQ ID NO:3) can be introduced as a

transgene into the genome of a non-human animal. Alternatively, a nonhuman homologue of the human dysferlin gene can be isolated based on hybridization to the human dysferlin sequence (e.g., cDNA) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the mutant dysferlin transgene in its genome and/or expression of the mutant dysferlin mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a mutant dysferlin can further be bred to other transgenic animals carrying other transgenes.

To create an homologously recombinant animal, a vector is prepared which contains at least a portion of a dysferlin gene into which a deletion, addition or substitution has been introduced to thereby alter a dysferlin gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous dysferlin gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous dysferlin gene is mutated

or otherwise altered (e.g., contains one of the mutations described in Table 2). In the homologous recombination vector, the altered portion of the dysferlin sequence is flanked at its 5' and 3' ends by additional nucleic acid of the dysferlin gene to allow for homologous recombination to occur between the exogenous dysferlin nucleic acid sequence carried by the vector and an endogenous dysferlin gene in an embryonic stem cell. The additional flanking dysferlin nucleic acid is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (*see, e.g.*, Thomas and Capecchi (1987) *Cell* 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced dysferlin sequence has homologously recombined with the endogenous dysferlin gene are selected (*see, e.g.*, Li et al. (1992) *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (e.g., a mouse) to form aggregation chimeras (*see, e.g.*, Bradley in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication Nos. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

Other Embodiments

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. An isolated DNA comprising a nucleotide sequence which hybridizes under stringent hybridization conditions to SEQ ID NO:3, or a complement thereof.

2. The isolated DNA of claim 1, wherein the nucleotide sequence is SEQ ID NO:117.

3. An isolated DNA comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:4-12.

4. The isolated DNA of claim 3, comprising the sequence of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, or SEQ ID NO:21.

5. An isolated DNA comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS:22-30.

6. A single stranded oligonucleotide of 14-50 nucleotides in length having a nucleotide sequence identical to a portion of SEQ ID NO:3, or a complement thereof.

7. A pair of PCR primers consisting of:

(a) a first single stranded oligonucleotide consisting of 14-50 contiguous nucleotides that are identical to a portion of SEQ ID NO:117; and

(b) a second single stranded oligonucleotide consisting of 14-50 contiguous nucleotides that are identical to a portion of SEQ ID NO:117, wherein the sequence of at least one of the oligonucleotides is identical to a portion of a strand of SEQ ID NO:3, and the first oligonucleotide is not complementary to the second oligonucleotide.

8. A pair of single-stranded oligonucleotides, wherein both oligonucleotides are selected from the group consisting of SEQ ID NOS:130-231, SEQ ID NO:110, and SEQ ID NO:112 and the oligonucleotides are different from each other.

9. An isolated DNA comprising a nucleotide sequence that encodes a polypeptide that shares at least 70% sequence identity with SEQ ID NO:2, or a complement of the nucleotide sequence.

10. The isolated DNA of claim 9, wherein the polypeptide comprises the sequence of SEQ ID NO:2.

11. An isolated DNA comprising a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid having a sequence selected from the group consisting of SEQ ID NOs:31-79 and 90-100.

12. A single stranded oligonucleotide of 14-50 nucleotides in length comprising a nucleotide sequence which is identical to a portion of a nucleic acid selected from the group consisting of SEQ ID NOs:31-79 and 90-100, or a complement of the nucleotide sequence.

13. The oligonucleotide of claim 12, wherein the portion includes an intronic sequence.

14. A pair of PCR primers consisting of:

(a) a first single-stranded oligonucleotide consisting of 14-50 contiguous nucleotides that are identical to a portion of a sense strand of a nucleic acid selected from the group consisting of SEQ ID NOs:31-85; and

(b) a second single stranded oligonucleotide consisting of 14-50 contiguous nucleotides that are identical to a portion of the antisense strand of a nucleic acid selected from the group consisting of SEQ ID NOs:31-85, wherein the sequence of at least one of the oligonucleotides comprises a sequence identical to a portion of a nucleic acid selected from SEQ ID NOs: 31-79 and 90-100, and wherein the first oligonucleotide is not complementary to the second oligonucleotide.

15. A pair of single-stranded oligonucleotides selected from the group consisting of SEQ ID NOs:101-116, SEQ ID NOs:184-185, SEQ ID NOs:188-191, SEQ ID NOs:210-213, and SEQ ID NOs:216-217.

16. A vector comprising the isolated DNA of claim 1.

17. A substantially pure polypeptide comprising an amino acid sequence sharing at least 70% sequence identity with SEQ ID NO:2.

18. The substantially pure polypeptide of claim 17, wherein the polypeptide comprises an amino acid sequence identical to that of a naturally occurring polypeptide.

19. The substantially pure polypeptide of claim 18, wherein the amino acid sequence comprises the sequence of SEQ ID NO:2.

20. A substantially pure polypeptide comprising an amino acid sequence identical to the amino acid sequence of amino acid residues 1-500, 501-1000, 1001-1500, or 1501-2080 of SEQ ID NO:2.

21. A substantially pure polypeptide comprising the amino acid sequence of SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88 or SEQ ID NO:89.

22. A substantially pure polypeptide selected from the group consisting of amino acids 253-403 of SEQ ID NO:2, amino acids 624-865 of SEQ ID NO:2, and amino acids 1664-1786 of SEQ ID NO:2.

23. A fusion protein comprising a polypeptide of claim 22.

24. An antibody that specifically binds to the polypeptide of claim 22.

25. An antibody that binds specifically to the polypeptide of claim 17.

26. A cell comprising the isolated DNA of claim 1.

27. A non-human mammal, the genomic DNA of which bears a transgene, wherein the transgene comprises the isolated DNA of claim 1.

28. A transgenic non-human mammal having a transgene disrupting or interfering with the expression of a dysferlin gene.

29. A method of decreasing the symptoms of muscular dystrophy in a mammal, the method comprising introducing into a cell of said mammal the isolated DNA of claim 1.

30. A method of decreasing the symptoms of muscular dystrophy in a mammal, the method comprising introducing

into a cell of said mammal the vector of claim 16, the vector being an expression vector.

31. A method of decreasing the symptoms of muscular dystrophy in a mammal, the method comprising introducing into a cell of said mammal the protein of claim 17.

32. A method for identifying a patient, a fetus, or a pre-embryo at risk for having a dysferlin-related disorder, the method comprising:

(a) obtaining a sample of genomic DNA from the patient, fetus, or pre-embryo; and

(b) determining whether the sample contains a mutation in a dysferlin gene, wherein a patient, a fetus, or a pre-embryo having a mutation in a dysferlin gene is at risk for having a dysferlin-related disorder.

33. The method of claim 32, comprising:

(a) treating the sample of genomic DNA with a restriction enzyme specific for a particular restriction enzyme site; and

(b) detecting the presence or absence of the particular restriction enzyme site in the sample of genomic DNA as an indication of the presence or absence of a particular mutation in the genomic DNA.

34. The method of claim 33, wherein the restriction enzyme is selected from the group consisting of Pst I, Fnu4H I, BamH I, BstY I, Ava II, HinP I, Fsp I, Mbo II, ScrF I, BstN I, Mae I, Bfa I, Dde I, Bpm I, Ban II, Ava II, and Sau96 I.

35. The method of claim 32, comprising subjecting the sample to polymerase chain reaction (PCR).

36. The method of claim 32, comprising:

(a) contacting a single stranded oligonucleotide with the sample of genomic DNA; and

(c) detecting hybridization or lack thereof between the single stranded oligonucleotide and the genomic DNA, as an indication of the presence or absence of a mutation in the genomic DNA.

37. A method for identifying a patient, a fetus, or a pre-embryo at risk for having a dysferlin-related disorder, said method comprising:

(a) providing a sample comprising dysferlin mRNA from the patient, fetus, or pre-embryo; and

(b) determining whether the dysferlin mRNA contains a mutation, wherein a patient, a fetus, or a pre-embryo having a dysferlin mRNA containing a mutation is at risk for having a dysferlin-related disorder.

38. The method of claim 37, wherein the presence or absence of the mutation is detected by Northern blot.

39. The method of claim 37, wherein the method includes the step of subjecting the sample to polymerase chain reaction (PCR).

40. A method for detecting the absence of a mutation in a dysferlin protein of a patient, a fetus, or a pre-embryo, the method comprising:

(a) providing a sample comprising a dysferlin protein of the patient, fetus, or pre-embryo;

(b) contacting the sample with the antibody of claim 22; and

(c) detecting binding of the antibody to dysferlin protein in the sample, if any, wherein binding indicates a normal dysferlin protein.

41. An isolated DNA comprising a nucleotide sequence that is identical to the sequence of amino acid residues 3501-3520 of SEQ ID NO:1, 3737-3756 of SEQ ID NO:1, 3842-3861 of SEQ ID NO:1, 5114-5139 of SEQ ID NO:1, or 5239-5255 of SEQ ID NO:1.

42. An isolated DNA comprising a nucleotide sequence selected from the group consisting of

3501-3520 of SEQ ID NO:1, wherein nucleotide G at 3510 is A;

3737-3756 of SEQ ID NO:1, wherein nucleotide G at 3746 is deleted;

3842-3861 of SEQ ID NO:1, wherein nucleotide C at 3851 is T;

5114-5139 of SEQ ID NO:1, wherein nucleotide C at 5122 and nucleotide A at 5123 are deleted;

5239-5255 of SEQ ID NO:1, wherein nucleotide G at 5245 is deleted and nucleotide G at 5249 is C; and

5239-5255 of SEQ ID NO:1, wherein nucleotide G at 5245 is C and nucleotide G at 5249 is deleted.

43. An isolated nucleic acid comprising a nucleotide sequence which hybridizes under stringent hybridization conditions to nucleic acids 3284-3720 of SEQ ID NO:232, or the complement of said nucleotide sequence.

44. An isolated nucleic acid comprising a nucleotide sequence identical to the sequence of nucleotides 3284-3720 of SEQ ID NO:232, or a complement of said nucleotide sequence.

45. The isolated nucleic acid of claim 44, wherein the nucleotide sequence comprises the sequence of SEQ ID NO:232 or the complement of SEQ ID NO:232.

46. An isolated polypeptide comprising:

a) at least 15 contiguous amino acids of the polypeptide comprising amino acids 1-24 of SEQ ID NO:233,

b) a naturally occuring allelic variant of a polypeptide comprising amino acids 1-24 of SEQ ID NO:233, or

c) an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes under stringent conditions to nucleotides 3284-3720 of SEQ ID NO:232.

47. The polypeptide of claim 46, wherein the polypeptide comprises SEQ ID NO:233.

48. A vector comprising the nucleic acid of claim 44.

49. A cell comprising the vector of claim 48.

50. A method of making a polypeptide, the method comprising culturing the cell of claim 49.

51. An antibody which specifically binds to a polypeptide of claim 46.

52. The antibody of claim 51, wherein the antibody binds to a polypeptide selected from the group comprising amino acids 253-403 of SEQ ID NO:233, amino acids 624-865 of SEQ ID NO:233, and amino acids 1664-1786 of SEQ ID NO:233.

53. The antibody of claim 51, wherein the antibody is a monclonal antibody.

54. The antibody of claim 51, wherein the antibody is a polyclonal antibody.

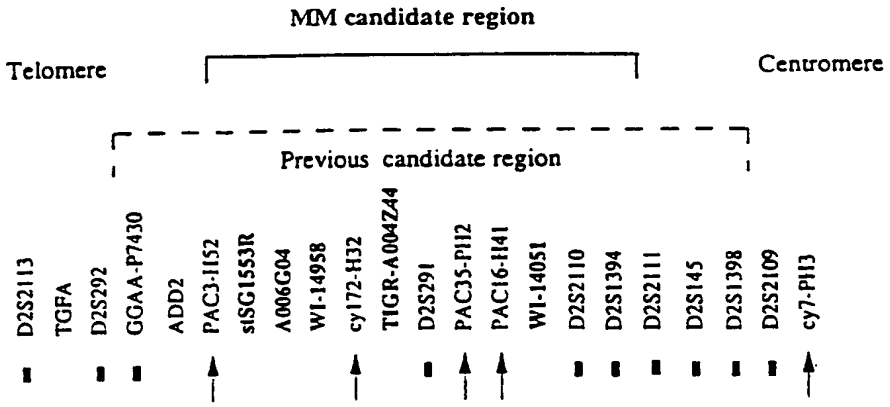

FIG. 1A

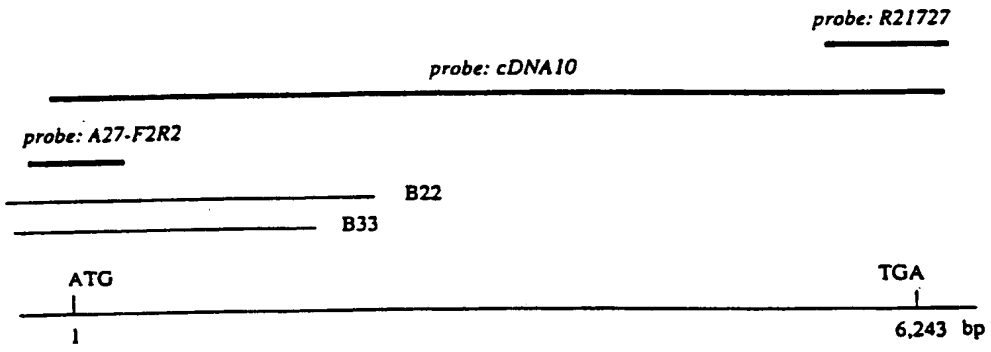

FIG. 1B

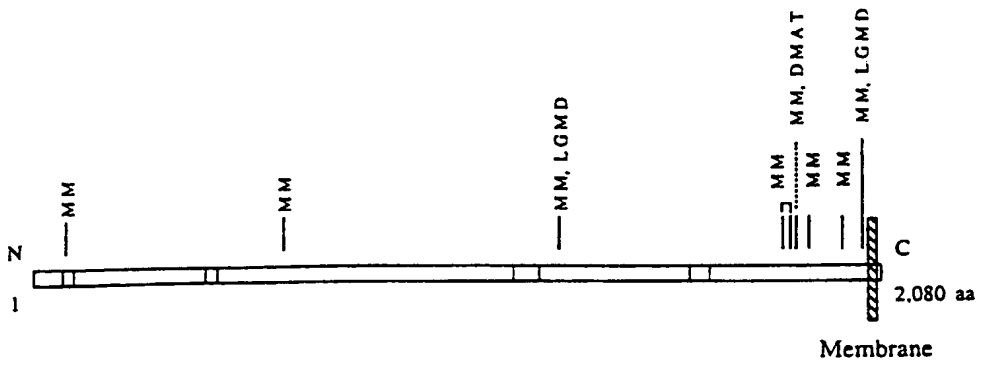

FIG. 1C

```
   1 MLRVEILYAE NVHTPDTDIS DAYCSAVFAG VKKRTKVIKN SVNPVWNEGF
  51 EWDLKGIPLD QGSELHVVVK DHETMGRNRF LGEAKVPLRE VLATPSLSAS
 101 FNAPLLDTKK QPTGASLVLQ VSYTPLPGAV PLFPPPTPLE PSPTLPDLDV
 151 VADTGGEEDT EDQGLTGDEA EPFLDQSGGP GAPTTPRKLP SRPPPHYPGI
 201 KRKRSAPTSR KLLSDKPQDF QIRVQVIEGR QLPGVNIKPV VKVTAAGQTK
 251 RTRIHKGNSP LFNETLFFNL FDSPGELFDE PIFITVVDSR SLRTDALLGE
 301 FRMDVGTIYR EPRHAYLRKW LLLSDPDDFS AGARGYLKTS LCVLGPGDEA
 351 PLERKDPSED KEDIESNLLR PTGVALRGAH FCLKVFRAED LPQMDDAVMD
 401 NVKQIFGFES NKKNLVDPFV EVSFAGKMLC SKILEKTANP QWNQNITLPA
 451 MFPSMCEKMR IRIIDWDRLT HNDIVATTYL SMSKISAPGG EIEEEPAGAV
 501 KPSKASDLDD YLGFLPTFGP CYINLYGSPR EFTGFPDPYT ELNTGKGEGV
 551 AYRGRLLLSL ETKLVEHSEQ KVEDLPADDI LRVEKYLRRR KYSLFAAFYS
 601 ATMLQDVDDA IQFEVSIGNY GNKFDMTCLP LASTTQYSRA VFDGCHYYYL
 651 PWGNVKPVVV LSSYWEDISH RIETQNQLLG IADRLEAGLE QVHLALKAQC
 701 STEDVDSLVA QLTDELIAGC SQPLGDIHET PSATHLDQYL YQLRTHHLSQ
 751 ITEAALALKL GHSELPAALE QAEDWLLRLR ALAEEPQNSL PDIVIWMLQG
 801 DKRVAYQRVP AHQVLFSRRG ANYCGKNCGK LQTIFLKYPM EKVPGARMPV
 851 QIRVKLWFGL SVDEKEFNQF AEGKLSVFAE TYENETKLAL VGNWGTTGLT
 901 YPKFSDVTGK IKLPKDSFRP SAGWTWAGDW FVCPEKTLLH DMDAGHLSFV
 951 EEVFENQTRL PGGQWIYMSD NYTDVNGEKV LPKDDIECPL GWKWEDEEWS
1001 TDLNRAVDEQ GWEYSITIPP ERKPKHWVPA EKMYYTHRRR RWVRLRRRDL
1051 SQMEALKRHR QAEAEGEGWE YASLFGWKFH LEYRKTDAFR RRRWRRRMEP
1101 LEKTGPAAVF ALEGALGGVM DDKSEDSMSV STLSFGVNRP TISCIFDYGN
1151 RYHLRCYMYQ ARDLAAMDKD SFSDPYAIVS FLHQSQKTVV VKNTLNPTWD
1201 QTLIFYEIEI FGEPATVAEQ PPSIVVELYD HDTYGADEFM GRCICQPSLE
1251 RMPRLAWFPL TRGSQPSGEL LASFELIQRE KPAIHHIPGF EVQETSRILD
1301 ESEDTDLPYP PPQREANIYM VPQNIKPALQ RTAIEILAWG LRNMKSYQLA
1351 NISSPSLVVE CGGQTVQSCV IRNLRKNPNF DICTLFMEVM LPREELYCPP
1401 ITVKVIDNRQ FGRRPVVGQC TIRSLESFLC DPYSAESPSP QGGPDDVSLL
1451 SPGEDVLIDI DDKEPLIPIQ EEEFIDWWSK FFASIGEREK CGSYLEKDFD
1501 TLKVYDTQLE NVEAFEGLSD FCNTFKLYRG KTQEETEDPS VIGEFKGLFK
1551 IYPLPEDPAI PMPPRQFHQL AAQGPQECLV RIYIVRAEGL QPKDPNGKCD
1601 PYIKISIGKK SVSDQDNYIP CTLEPVFGKM FELTCTLPLE KDLKITLYDY
1651 DLLSKDEKIG ETVVDLENRL LSKFGARCGL PQTYCVSGPN QWRDQLRPSQ
1701 LLHLFCQQHR VKAPVYRTDR VMFQDKEYSI EEIEAGRIPN PHLGPVEERL
1751 ALHVLQQQGL VPEHVESRPL YSPLQPDIEQ GKLQMWVDLF PKALGRPGPP
1801 FNITPRRARR FFLRCIIWNT RDVILDDLSL TGEKMSDIYV KGWMIGFEEH
1851 KQKTDVHYRS LGGEGNFNWR FIFPFDYLPA EQVCTIAKKD AFWRLDKTES
1901 KIPARVVFQI WDNDKFSFDD FLGSLQLDLN RMPKPAKTAK KCSLDQLDDA
1951 FHPEWFVSLF EQKTVKGWWP CVAEEGEKKI LAGKLEMTLE IVAESEHEER
2001 PAGQGRDEPN MNPKLEDPRR PDTSFLWFTS PYKTMKFILW RRFRWAIILF
2051 IILFILLLFL AIFIYAFPNY AAMKLVKPES
```

(SEQ ID NO: 2)

FIG. 2

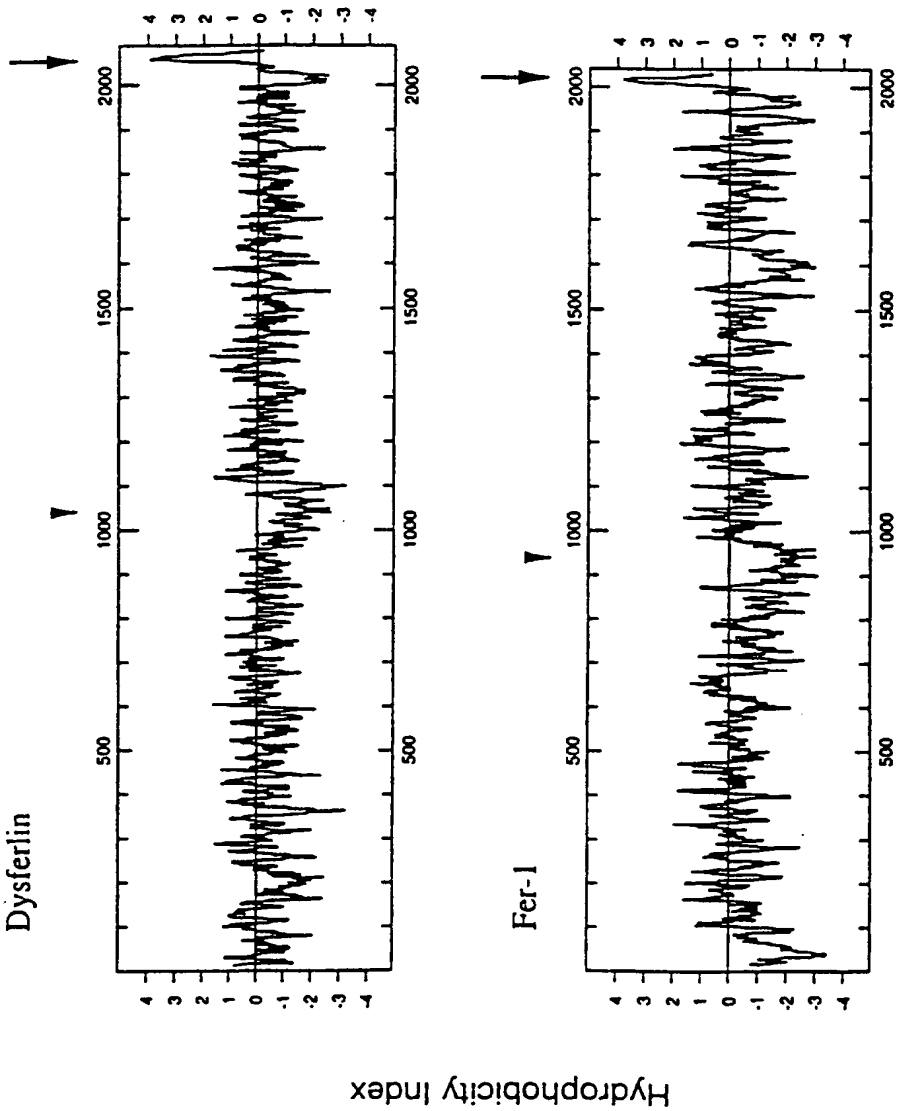

FIG. 3

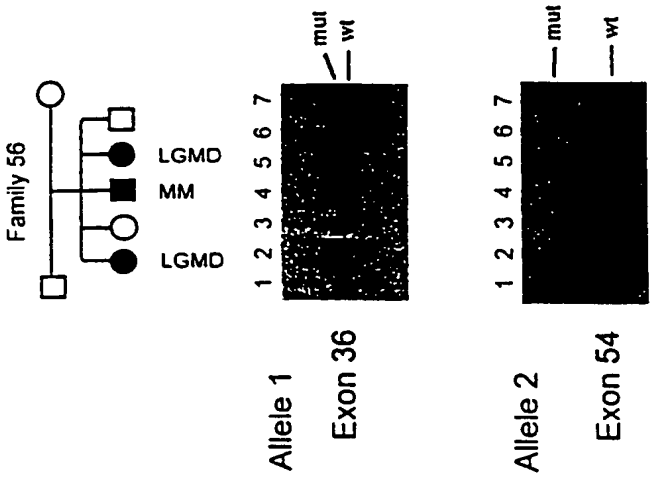

FIG. 4

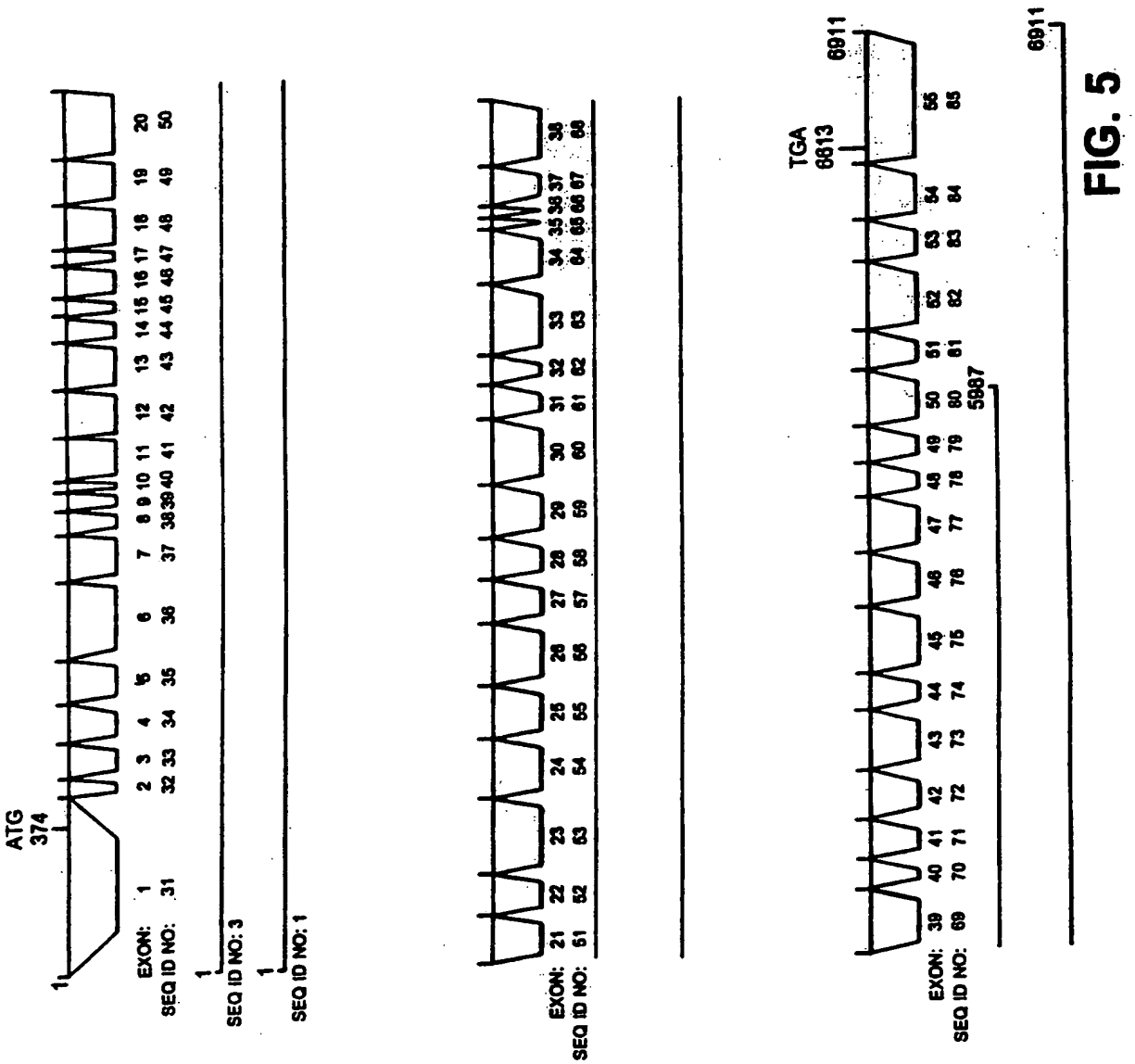

FIG. 5

```
1/1                                                 31/11                                                 61/21
TCC TGG TTC AAG CGA TTC TCT GGC CTC AGC CTC CCG AGT AGC TGG GAT TAC AGG CAT GCT CCA CCA AGC CCG GGT AAT TTT GTA TTT TTA
S   W   F   K   R   F   S   G   L   S   L   P   S   S   W   D   Y   R   H   A   P   P   S   P   G   N   F   V   F   L
91/31                                               121/41                                                151/51
ATA GAG ACG GGG TTT TGC CAT GTT GGT CAG GCT GGT CTC GAA CTC CTG ACC TCA GGT GAT CTG CCC ACC TTG GCC TCC CAA CGT GCT GAG
I   E   T   G   F   C   H   V   G   Q   A   G   L   E   L   L   T   S   G   D   L   P   T   L   A   S   Q   R   A   E
181/61                                              211/71                                                241/81
ATT ACA GGC ATG AGT CAC TGT GCC CGG CAG AGA TGG TCT AAT TCA TAT GAA AGA ACT CTG AAA AAA GTA GAA AGT GAT TTT CTA AAA TAA
I   T   G   M   S   H   C   A   R   Q   R   W   S   N   S   Y   E   R   T   L   K   K   V   E   S   D   F   L   K   *
271/91                                              301/101                                               331/111
GGT ACA AAT AAT TAA TGT AAG CAT AAT CAC CTA ACC TTG TGG AAT TTT TTT TTT TTG AGA AGC AAA TTG CAA ATT TGT GAT AGA TCT AAA
G   T   N   N   *   C   K   H   N   H   L   T   L   W   N   F   F   F   L   R   S   K   L   Q   I   C   D   R   S   K
361/121                                             391/131                                               421/141
GGA GAT TGA CTA AGA GGG TGA CCA TCT GGA AAT GAC GTC ATG TGA GAA TGG TTA AAG ATG CTC GGG AGA TTG AGC CTA GAG AAA GGA AGA
G   D   *   L   R   G   *   P   S   G   N   D   V   M   *   E   W   L   K   M   L   G   R   L   S   L   E   K   G   R
451/151                                             481/161                                               511/171
TTT GTG AAC CCA GGA GGC AGA GGT AGA GAT CCA GGA GAG ggc ggc gtg atg gat gac aag agt gaa gat tcc atg tcc gtc tcc acc ttg
F   V   N   P   G   G   R   G   R   D   P   G   E   G   G   V   M   D   D   K   S   E   D   S   M   S   V   S   T   L
541/181                                             571/191                                               601/201
agc ttc ggt gtg aac aga ccc acg att tcc tgc ata ttc gac tat ggg aac cgc tac cat cta cgc tgc tac atg tac cag gcc cgg gac
S   F   G   V   N   R   P   T   I   S   C   I   F   D   Y   G   N   R   Y   H   L   R   C   Y   M   Y   Q   A   R   D
631/211                                             661/221                                               691/231
ctg gct gcg atg gac aag gac tct ttt tct gat ccc tat gcc atc gtc tcc ttc ctg cac cag agc cag aag acg gtg gtg gtg aag aac
L   A   A   M   D   K   D   S   F   S   D   P   Y   A   I   V   S   F   L   H   Q   S   Q   K   T   V   V   V   K   N
721/241                                             751/251                                               781/261
acc ctt aac ccc acc tgg gac cag acg ctc atc ttc tac gag atc gag atc ttt ggc gag ccg gcc aca gtt gct gag caa ccg ccc agc
T   L   N   P   T   W   D   Q   T   L   I   F   Y   E   I   E   I   F   G   E   P   A   T   V   A   E   Q   P   P   S
811/271                                             841/281                                               871/291
att gtg gtg gag ctg tac gac cat gac act tat ggt gca gac gag ttt atg ggt cgc tgc atc tgt caa ccg agt ctg gaa cgg atg cca
I   V   V   E   L   Y   D   H   D   T   Y   G   A   D   E   F   M   G   R   C   I   C   Q   P   S   L   E   R   M   P
901/301                                             931/311                                               961/321
cgg ctg gcc tgg ttc cca ctg acg agg ggc agc cag ccg tcg ggg gag ctg ctg gcc tct ttt gag ctc atc cag aga gag aag ccg gcc
R   L   A   W   F   P   L   T   R   G   S   Q   P   S   G   E   L   L   A   S   F   E   L   I   Q   R   E   K   P   A
991/331                                             1021/341                                              1051/351
atc cac cat att cct ggt ttt gag gtg cag gag aca tca agg atc ctg gat gag tct gag gac aca gac ctg ccc tac cca cca ccc cag
I   H   H   I   P   G   F   E   V   Q   E   T   S   R   I   L   D   E   S   E   D   T   D   L   P   Y   P   P   P   Q
1081/361                                            1111/371                                              1141/381
agg gag gcc aac atc tac atg gtt cct cag aac atc aag cca gcg ctc cag cgt acc gcc atc gag atc ctg gca tgg ggc ctg cgg aac
R   E   A   N   I   Y   M   V   P   Q   N   I   K   P   A   L   Q   R   T   A   I   E   I   L   A   W   G   L   R   N
1171/391                                            1201/401                                              1231/411
atg aag agt tac cag ctg gcc aac atc tcc tcc ccc agc ctc gtg gta gag tgt ggg ggc cag acg gtg cag tcc tgt gtc atc agg aac
M   K   S   Y   Q   L   A   N   I   S   S   P   S   L   V   V   E   C   G   G   Q   T   V   Q   S   C   V   I   R   N
1261/421                                            1291/431                                              1321/441
ctc cgg aag aac ccc aac ttt gac atc tgc acc ctc ttc atg gaa gtg atg ctg ccc agg gag gag ctc tac tgc ccc ccc atc acc gtc
L   R   K   N   P   N   F   D   I   C   T   L   F   M   E   V   M   L   P   R   E   E   L   Y   C   P   P   I   T   V
1351/451                                            1381/461                                              1411/471
aag gtc atc gat aac cgc cag ttt ggc cgc cgg cct gtg gtg ggc cag tgt acc atc cgc tcc ctg gag agc ttc ctg tgt gac ccc tac
K   V   I   D   N   R   Q   F   G   R   R   P   V   V   G   Q   C   T   I   R   S   L   E   S   F   L   C   D   P   Y
1441/481                                            1471/491                                              1501/501
tcg gcg gag agt cca tcc cca cag ggt ggc cca gac gat gtg agc cta ctc agt cct ggg gaa gac gtg ctc atc gac att gat gac aag
S   A   E   S   P   S   P   Q   G   G   P   D   D   V   S   L   L   S   P   G   E   D   V   L   I   D   I   D   D   K
1531/511                                            1561/521                                              1591/531
gag ccc ctc atc ccc atc cag gag gaa gag ttc atc gat tgg tgg agc aaa ttc ttt gcc tcc ata ggg gag agg gaa aag tgc ggc tcc
E   P   L   I   P   I   Q   E   E   E   F   I   D   W   W   S   K   F   F   A   S   I   G   E   R   E   K   C   G   S
1621/541                                            1651/551                                              1681/561
tac ctg gag aag gat ttt gac acc ctg aag gtc tat gac aca cag ctg gag aat gtg gag gcc ttt gag ggc ctg tct gac ttt tgt aac
Y   L   E   K   D   F   D   T   L   K   V   Y   D   T   Q   L   E   N   V   E   A   F   E   G   L   S   D   F   C   N
1711/571                                            1741/581                                              1771/591
acc ttc aag ctg tac cgg ggc aag acg cag gag gag aca gaa gat cca tct gtg att ggt gaa ttt aag ggc ctc ttc aaa att tat ccc
T   F   K   L   Y   R   G   K   T   Q   E   E   T   E   D   P   S   V   I   G   E   F   K   G   L   F   K   I   Y   P
1801/601                                            1831/611                                              1861/621
ctc cca gaa gac cca gcc atc ccc atg ccc cca aga cag ttc cac cag ctg gcc gcc cag gga ccc cag gag tgc ttg gtc cgt atc tac
L   P   E   D   P   A   I   P   M   P   P   R   Q   F   H   Q   L   A   A   Q   G   P   Q   E   C   L   V   R   I   Y
1891/631                                            1921/641                                              1951/651
att gtc cga gca ttt ggc ctg cag ccc aag gac ccc aat gga aag tgt gat cct tac atc aag atc tcc ata ggg aag aaa tca gtg agt
I   V   R   A   F   G   L   Q   P   K   D   P   N   G   K   C   D   P   Y   I   K   I   S   I   G   K   K   S   V   S
1981/661                                            2011/671                                              2041/681
gac cag gat aac tac atc ccc tgc acg ctg gag ccc gta ttt gga aag atg ttc gag ctg acc tgc act ctg cct ctg gag aag gac cta
D   Q   D   N   Y   I   P   C   T   L   E   P   V   F   G   K   M   F   E   L   T   C   T   L   P   L   E   K   D   L
2071/691                                            2101/701                                              2131/711
aag atc act ctc tat gac tat gac ctc ctc tcc aag gac gaa aag atc ggt gag acg gtc gtc gac ctg gag aac agg ctg ctg tcc aag
K   I   T   L   Y   D   Y   D   L   L   S   K   D   E   K   I   G   E   T   V   V   D   L   E   N   R   L   L   S   K
2161/721                                            2191/731                                              2221/741
ttt ggg gct cgc tgt gga ctc cca cag acc tac tgt gtc tct gga ccg aac cag tgg cgg gac cag ctc cgc ccc tcc cag ctc ctc cac
F   G   A   R   C   G   L   P   Q   T   Y   C   V   S   G   P   N   Q   W   R   D   Q   L   R   P   S   Q   L   L   H
2251/751                                            2281/761                                              2311/771
ctc ttc tgc cag cag cat aga gtc aag gca cct gtg tac cgg aca gac cgt gta atg ttt cag gat aaa gaa tat tcc att gaa gag ata
L   F   C   Q   Q   H   R   V   K   A   P   V   Y   R   T   D   R   V   M   F   Q   D   K   E   Y   S   I   E   E   I
2341/781                                            2371/791                                              2401/801
gag gct ggc agg atc cca aac cca cac ctg ggc cca gtg gag gag cgt ctg gct ctg cat gtg ctt cag cag cag ggc ctg gtc ccg gag
E   A   G   R   I   P   N   P   H   L   G   P   V   E   E   R   L   A   L   H   V   L   Q   Q   Q   G   L   V   P   E
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Figure 6A

```
2431/811                                                2461/821                                                2491
cac gtg gag tca cgg ccc ctc tac [redacted] ccc ctg cag cca gac atc gag cag ggg aag ctg cag a[redacted] tgg gtc gac cta ttt ccg aag gcc
H   V   E   S   R   P   L   Y   S   P   L   Q   P   D   I   E   Q   G   K   L   Q   M   W   V   D   L   F   P   K   A
2521/841                                                2551/851                                                2581/861
ctg ggg cgg cct gga cct ccc ttc aac atc acc cca cgg aga gcc aga agg ttt ttc ctg cgt tgt att atc tgg aat acc aga gat gtg
L   G   R   P   G   P   P   F   N   I   T   P   R   R   A   R   R   F   F   L   R   C   I   I   W   N   T   R   D   V
2611/871                                                2641/881                                                2671/891
atc ctg gat gac ctg agc ctc acg ggg gag aag atg agc gac att tat gtg aaa ggt tgg atg att ggc ttt gaa gaa cac aag caa aag
I   L   D   D   L   S   L   T   G   E   K   M   S   D   I   Y   V   K   G   W   M   I   G   F   E   E   H   K   Q   K
2701/901                                                2731/911                                                2761/921
aca gac gtg cat tat cgt tcc ctg gga ggt gaa ggc aac ttc aac tgg agg ttc att ttc ccc ttc gac tac ctg cca gct gag caa gtc
T   D   V   H   Y   R   S   L   G   G   E   G   N   F   N   W   R   F   I   F   P   F   D   Y   L   P   A   E   Q   V
2791/931                                                2821/941                                                2851/951
tgt acc att gcc aag aag gat gcc ttc tgg agg ctg gac aag act gag agc aaa atc cca gca cga gtg gtg ttc cag atc tgg gac aat
C   T   I   A   K   K   D   A   F   W   R   L   D   K   T   E   S   K   I   P   A   R   V   V   F   Q   I   W   D   N
2881/961                                                2911/971                                                2941/981
gac aag ttc tcc ttt gat gat ttt ctg ggc tcc ctg cag ctc gat ctc aac cgc atg ccc aag cca gcc aag aca gcc aag aag tgc tcc
D   K   F   S   F   D   D   F   L   G   S   L   Q   L   D   L   N   R   M   P   K   P   A   K   T   A   K   K   C   S
2971/991                                                3001/1001                                               3031/1011
ttg gac cag ctg gat gat gct ttc cac cca gaa tgg ttt gtg tcc ctt ttt gag cag aaa aca gtg aag ggc tgg tgg ccc tgt gta gca
L   D   Q   L   D   D   A   F   H   P   E   W   F   V   S   L   F   E   Q   K   T   V   K   G   W   W   P   C   V   A
3061/1021                                               3091/1031                                               3121/1041
gaa gag ggt gag aag aaa ata ctg gcg ggc aag ctg gaa atg acc ttg gag att gta gca gag agt gag cat gag gag cgg cct gct ggc
E   E   G   E   K   K   I   L   A   G   K   L   E   M   T   L   E   I   V   A   E   S   E   H   E   E   R   P   A   G
3151/1051                                               3181/1061                                               3211/1071
cag ggc cgg gat gag ccc aac atg aac cct aag ctt gag gac cca agg cgc ccc gac acc tcc ttc ctg tgg ttt acc tcc cca tac aag
Q   G   R   D   E   P   N   M   N   P   K   L   E   D   P   R   R   P   D   T   S   F   L   W   F   T   S   P   Y   K
3241/1081                                               3271/1091                                               3301/1101
acc atg aag ttc atc ctg tgg cgg cgt ttc cgg tgg gcc atc atc ctc ttc atc atc ctc ttc atc ctg ctg ctg ttc ctg gcc atc ttc
T   M   K   F   I   L   W   R   R   F   R   W   A   I   I   L   F   I   I   L   F   I   L   L   L   F   L   A   I   F
3331/1111                                               3361/1121                                               3391/1131
atc tac gcc ttc ccg aac tat gct gcc atg aag ctg gtg aag ccc ttc agc tga gga ctc tcc tgc cct gta gaa ggg gcc gtg ggg tcc
I   Y   A   F   P   N   Y   A   A   M   K   L   V   K   P   F   S   *   G   L   S   C   P   V   E   G   A   V   G   S
3421/1141                                               3451/1151                                               3481/1161
cct cca gca tgg gac tgg cct gcc tcc tcc gcc cag ctc ggc gag ctc ctc cag acc tcc tag gcc tga ttg tcc tgc cag ggt ggg cag
P   P   A   W   D   W   P   A   S   S   A   Q   L   G   E   L   L   Q   T   S   *   A   *   L   S   C   Q   G   G   Q
3511/1171                                               3541/1181                                               3571/1191
aca gac aga tgg acc ggc cca cac tcc cag agt tgc taa cat gga gct ctg aga tca ccc cac ttc cat cat ttc ctt ctc ccc caa ccc
T   D   R   W   T   G   P   H   S   Q   S   C   *   H   G   A   L   R   S   P   H   F   H   H   F   L   L   P   Q   P
3601/1201                                               3631/1211                                               3661/1221
aac gct ttt ttg gat cag ctc aga cat att tca gta taa aac agt tgg aac cac aaa aaa aaa aaa aaa aa  (SEQ ID NO:232)
N   A   F   L   D   Q   L   R   H   I   S   V   *   N   S   W   N   H   K   K   K   K   K      (SEQ ID NO:233)
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Figure 6B

SEQUENCE LISTING

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<120> DYSFERLIN, A GENE MUTATED IN DISTAL MYOPATHY AND LIMB GIRDLE MUSCULAR DYSTROPHY

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tgttctcgga acgccggctg acaagcgggg tgagcgcagg cggggcgggg acccagccta    180
gcccactgga gcagccgggg gtggcccgtt ccccttaag agcaactgct ctaagccagg     240
agccagagat tcgagccggc ctcgcccagc cagccctctc cagcgagggg acccacaagc    300
ggcgcctcgg ccctcccgac ctttccgagc cctctttgcg ccctgggcgc acggggccct    360
acacgcgcca agc atg ctg agg gtc ttc atc ctc tat gcc gag aac gtc        409
                Met Leu Arg Val Phe Ile Leu Tyr Ala Glu Asn Val
                  1               5                  10

cac aca ccc gac acc gac atc agc gat gcc tac tgc tcc gcg gtg ttt      457
His Thr Pro Asp Thr Asp Ile Ser Asp Ala Tyr Cys Ser Ala Val Phe
          15                  20                  25

gca ggg gtg aag aag aga acc aaa gtc atc aag aac agc gtg aac cct      505
Ala Gly Val Lys Lys Arg Thr Lys Val Ile Lys Asn Ser Val Asn Pro
      30                  35                  40

gta tgg aat gag gga ttt gaa tgg gac ctc aag ggc atc ccc ctg gac      553
Val Trp Asn Glu Gly Phe Glu Trp Asp Leu Lys Gly Ile Pro Leu Asp
  45                  50                  55                  60

cag ggc tct gag ctt cat gtg gtg gtc aaa gac cat gag acg atg ggg      601
Gln Gly Ser Glu Leu His Val Val Val Lys Asp His Glu Thr Met Gly
                  65                  70                  75

agg aac agg ttc ctg ggg gaa gcc aag gtc cca ctc cga gag gtc ctc      649
Arg Asn Arg Phe Leu Gly Glu Ala Lys Val Pro Leu Arg Glu Val Leu
              80                  85                  90

gcc acc cct agt ctg tcc gcc agc ttc aat gcc ccc ctg ctg gac acc      697
Ala Thr Pro Ser Leu Ser Ala Ser Phe Asn Ala Pro Leu Leu Asp Thr
          95                  100                 105

aag aag cag ccc aca ggg gcc tcg ctg gtc ctg cag gtg tcc tac aca      745
Lys Lys Gln Pro Thr Gly Ala Ser Leu Val Leu Gln Val Ser Tyr Thr
      110                 115                 120
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ccg ctg cct gga gct gtg ccc ctg ttc ccg ccc cct act cct ctg gag      793
Pro Leu Pro Gly Ala Val Pro Leu Phe Pro Pro Pro Thr Pro Leu Glu
125                 130                 135                 140

ccc tcc ccg act ctg cct gac ctg gat gta gtg gca gac aca gga gga      841
Pro Ser Pro Thr Leu Pro Asp Leu Asp Val Val Ala Asp Thr Gly Gly
                145                 150                 155

gag gaa gac aca gag gac cag gga ctc act gga gat gag gcg gag cca      889
Glu Glu Asp Thr Glu Asp Gln Gly Leu Thr Gly Asp Glu Ala Glu Pro
            160                 165                 170

ttc ctg gat caa agc gga ggc ccg ggg gct ccc acc acc cca agg aaa      937
Phe Leu Asp Gln Ser Gly Gly Pro Gly Ala Pro Thr Thr Pro Arg Lys
        175                 180                 185

cta cct tca cgt cct ccg ccc cac tac ccc ggg atc aaa aga aag cga      985
Leu Pro Ser Arg Pro Pro Pro His Tyr Pro Gly Ile Lys Arg Lys Arg
    190                 195                 200

agt gcg cct aca tct aga aag ctg ctg tca gac aaa ccg cag gat ttc     1033
Ser Ala Pro Thr Ser Arg Lys Leu Leu Ser Asp Lys Pro Gln Asp Phe
205                 210                 215                 220

cag atc agg gtc cag gtg atc gag ggg cgc cag ctg ccg ggg gtg aac     1081
Gln Ile Arg Val Gln Val Ile Glu Gly Arg Gln Leu Pro Gly Val Asn
                225                 230                 235

atc aag cct gtg gtc aag gtt acc gct gca ggg cag acc aag cgg acg     1129
Ile Lys Pro Val Val Lys Val Thr Ala Ala Gly Gln Thr Lys Arg Thr
            240                 245                 250

cgg atc cac aag gga aac agc cca ctc ttc aat gag act ctt ttc ttc     1177
Arg Ile His Lys Gly Asn Ser Pro Leu Phe Asn Glu Thr Leu Phe Phe
        255                 260                 265

aac ttg ttt gac tct cct ggg gag ctg ttt gat gag ccc atc ttt atc     1225
Asn Leu Phe Asp Ser Pro Gly Glu Leu Phe Asp Glu Pro Ile Phe Ile
    270                 275                 280

acg gtg gta gac tct cgt tct ctc agg aca gat gct ctc ctc ggg gag     1273
Thr Val Val Asp Ser Arg Ser Leu Arg Thr Asp Ala Leu Leu Gly Glu
285                 290                 295                 300

ttc cgg atg gac gtg ggc acc att tac aga gag ccc cgg cac gcc tat     1321
Phe Arg Met Asp Val Gly Thr Ile Tyr Arg Glu Pro Arg His Ala Tyr
                305                 310                 315

ctc agg aag tgg ctg ctg ctc tca gac cct gat gac ttc tct gct ggg     1369
Leu Arg Lys Trp Leu Leu Leu Ser Asp Pro Asp Asp Phe Ser Ala Gly
            320                 325                 330

gcc aga ggc tac ctg aaa aca agc ctt tgt gtg ctg ggg cct ggg gac     1417
Ala Arg Gly Tyr Leu Lys Thr Ser Leu Cys Val Leu Gly Pro Gly Asp
        335                 340                 345

gaa gcg cct ctg gag aga aaa gac ccc tct gaa gac aag gag gac att     1465
Glu Ala Pro Leu Glu Arg Lys Asp Pro Ser Glu Asp Lys Glu Asp Ile
    350                 355                 360

gaa agc aac ctg ctc cgg ccc aca ggc gta gcc ctg cga gga gcc cac     1513
Glu Ser Asn Leu Leu Arg Pro Thr Gly Val Ala Leu Arg Gly Ala His
365                 370                 375                 380

ttc tgc ctg aag gtc ttc cgg gcc gag gac ttg ccg cag atg gac gat     1561
Phe Cys Leu Lys Val Phe Arg Ala Glu Asp Leu Pro Gln Met Asp Asp
                385                 390                 395
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gcc gtg atg gac aac gtg aaa cag atc ttt ggc ttc gag agt aac aag      1609
Ala Val Met Asp Asn Val Lys Gln Ile Phe Gly Phe Glu Ser Asn Lys
            400                 405                 410

aag aac ttg gtg gac ccc ttt gtg gag gtc agc ttt gcg ggg aaa atg      1657
Lys Asn Leu Val Asp Pro Phe Val Glu Val Ser Phe Ala Gly Lys Met
        415                 420                 425

ctg tgc agc aag atc ttg gag aag acg gcc aac cct cag tgg aac cag      1705
Leu Cys Ser Lys Ile Leu Glu Lys Thr Ala Asn Pro Gln Trp Asn Gln
    430                 435                 440

aac atc aca ctg cct gcc atg ttt ccc tcc atg tgc gaa aaa atg agg      1753
Asn Ile Thr Leu Pro Ala Met Phe Pro Ser Met Cys Glu Lys Met Arg
445                 450                 455                 460

att cgt atc ata gac tgg gac cgc ctg act cac aat gac atc gtg gct      1801
Ile Arg Ile Ile Asp Trp Asp Arg Leu Thr His Asn Asp Ile Val Ala
                465                 470                 475

acc acc tac ctg agt atg tcg aaa atc tct gcc cct gga gga gaa ata      1849
Thr Thr Tyr Leu Ser Met Ser Lys Ile Ser Ala Pro Gly Gly Glu Ile
            480                 485                 490

gaa gag gag cct gca ggt gct gtc aag cct tcg aaa gcc tca gac ttg      1897
Glu Glu Glu Pro Ala Gly Ala Val Lys Pro Ser Lys Ala Ser Asp Leu
        495                 500                 505

gat gac tac ctg ggc ttc ctc ccc act ttt ggg ccc tgc tac atc aac      1945
Asp Asp Tyr Leu Gly Phe Leu Pro Thr Phe Gly Pro Cys Tyr Ile Asn
    510                 515                 520

ctc tat ggc agt ccc aga gag ttc aca ggc ttc cca gac ccc tac aca      1993
Leu Tyr Gly Ser Pro Arg Glu Phe Thr Gly Phe Pro Asp Pro Tyr Thr
525                 530                 535                 540

gag ctc aac aca ggc aag ggg gaa ggt gtg gct tat cgt ggc cgg ctt      2041
Glu Leu Asn Thr Gly Lys Gly Glu Gly Val Ala Tyr Arg Gly Arg Leu
                545                 550                 555

ctg ctc tcc ctg gag acc aag ctg gtg gag cac agt gaa cag aag gtg      2089
Leu Leu Ser Leu Glu Thr Lys Leu Val Glu His Ser Glu Gln Lys Val
            560                 565                 570

gag gac ctt cct gcg gat gac atc ctc cgg gtg gag aag tac ctt agg      2137
Glu Asp Leu Pro Ala Asp Asp Ile Leu Arg Val Glu Lys Tyr Leu Arg
        575                 580                 585

agg cgc aag tac tcc ctg ttt gcg gcc ttc tac tca gcc acc atg ctg      2185
Arg Arg Lys Tyr Ser Leu Phe Ala Ala Phe Tyr Ser Ala Thr Met Leu
    590                 595                 600

cag gat gtg gat gat gcc atc cag ttt gag gtc agc atc ggg aac tac      2233
Gln Asp Val Asp Asp Ala Ile Gln Phe Glu Val Ser Ile Gly Asn Tyr
605                 610                 615                 620

ggg aac aag ttc gac atg acc tgc ctg ccg ctg gcc tcc acc act cag      2281
Gly Asn Lys Phe Asp Met Thr Cys Leu Pro Leu Ala Ser Thr Thr Gln
                625                 630                 635

tac agc cgt gca gtc ttt gac ggg tgc cac tac tac tac cta ccc tgg      2329
Tyr Ser Arg Ala Val Phe Asp Gly Cys His Tyr Tyr Tyr Leu Pro Trp
            640                 645                 650
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ggt aac gtg aaa cct gtg gtg gtg ctg tca tcc tac tgg gag gac atc      2377
Gly Asn Val Lys Pro Val Val Val Leu Ser Ser Tyr Trp Glu Asp Ile
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agc cat aga atc gag act cag aac cag ctg ctt ggg att gct gac cgg      2425
Ser His Arg Ile Glu Thr Gln Asn Gln Leu Leu Gly Ile Ala Asp Arg
    670                 675                 680

ctg gaa gct ggc ctg gag cag gtc cac ctg gcc ctg aag gcg cag tgc      2473
Leu Glu Ala Gly Leu Glu Gln Val His Leu Ala Leu Lys Ala Gln Cys
685                 690                 695                 700

tcc acg gag gac gtg gac tcg ctg gtg gct cag ctg acg gat gag ctc      2521
Ser Thr Glu Asp Val Asp Ser Leu Val Ala Gln Leu Thr Asp Glu Leu
                705                 710                 715

atc gca ggc tgc agc cag cct ctg ggt gac atc cat gag aca ccc tct      2569
Ile Ala Gly Cys Ser Gln Pro Leu Gly Asp Ile His Glu Thr Pro Ser
            720                 725                 730

gcc acc cac ctg gac cag tac ctg tac cag ctg cgc acc cat cac ctg      2617
Ala Thr His Leu Asp Gln Tyr Leu Tyr Gln Leu Arg Thr His His Leu
        735                 740                 745

agc caa atc act gag gct gcc ctg gcc ctg aag ctc ggc cac agt gag      2665
Ser Gln Ile Thr Glu Ala Ala Leu Ala Leu Lys Leu Gly His Ser Glu
    750                 755                 760

ctc cct gca gct ctg gag cag gcg gag gac tgg ctc ctg cgt ctg cgt      2713
Leu Pro Ala Ala Leu Glu Gln Ala Glu Asp Trp Leu Leu Arg Leu Arg
765                 770                 775                 780

gcc ctg gca gag gag ccc cag aac agc ctg ccg gac atc gtc atc tgg      2761
Ala Leu Ala Glu Glu Pro Gln Asn Ser Leu Pro Asp Ile Val Ile Trp
                785                 790                 795

atg ctg cag gga gac aag cgt gtg gca tac cag cgg gtg ccc gcc cac      2809
Met Leu Gln Gly Asp Lys Arg Val Ala Tyr Gln Arg Val Pro Ala His
            800                 805                 810

caa gtc ctc ttc tcc cgg cgg ggt gcc aac tac tgt ggc aag aat tgt      2857
Gln Val Leu Phe Ser Arg Arg Gly Ala Asn Tyr Cys Gly Lys Asn Cys
        815                 820                 825

ggg aag cta cag aca atc ttt ctg aaa tat ccg atg gag aag gtg cct      2905
Gly Lys Leu Gln Thr Ile Phe Leu Lys Tyr Pro Met Glu Lys Val Pro
    830                 835                 840

ggc gcc cgg atg cca gtg cag ata cgg gtc aag ctg tgg ttt ggg ctc      2953
Gly Ala Arg Met Pro Val Gln Ile Arg Val Lys Leu Trp Phe Gly Leu
845                 850                 855                 860

tct gtg gat gag aag gag ttc aac cag ttt gct gag ggg aag ctg tct      3001
Ser Val Asp Glu Lys Glu Phe Asn Gln Phe Ala Glu Gly Lys Leu Ser
                865                 870                 875

gtc ttt gct gaa acc tat gag aac gag act aag ttg gcc ctt gtt ggg      3049
Val Phe Ala Glu Thr Tyr Glu Asn Glu Thr Lys Leu Ala Leu Val Gly
            880                 885                 890

aac tgg ggc aca acg ggc ctc acc tac ccc aag ttt tct gac gtc acg      3097
Asn Trp Gly Thr Thr Gly Leu Thr Tyr Pro Lys Phe Ser Asp Val Thr
        895                 900                 905

ggc aag atc aag cta ccc aag gac agc ttc cgc ccc tcg gcc ggc tgg      3145
Gly Lys Ile Lys Leu Pro Lys Asp Ser Phe Arg Pro Ser Ala Gly Trp
    910                 915                 920
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acc tgg gct gga gat tgg ttc gtg tgt ccg gag aag act ctg ctc cat      3193
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925                 930                 935                 940

gac atg gac gcc ggt cac ctg agc ttc gtg gaa gag gtg ttt gag aac      3241
Asp Met Asp Ala Gly His Leu Ser Phe Val Glu Glu Val Phe Glu Asn
                945                 950                 955

cag acc cgg ctt ccc gga ggc cag tgg atc tac atg agt gac aac tac      3289
Gln Thr Arg Leu Pro Gly Gly Gln Trp Ile Tyr Met Ser Asp Asn Tyr
            960                 965                 970

acc gat gtg aac ggg gag aag gtg ctt ccc aag gat gac att gag tgc      3337
Thr Asp Val Asn Gly Glu Lys Val Leu Pro Lys Asp Asp Ile Glu Cys
        975                 980                 985

cca ctg ggc tgg aag tgg gaa gat gag gaa tgg tcc aca gac ctc aac      3385
Pro Leu Gly Trp Lys Trp Glu Asp Glu Glu Trp Ser Thr Asp Leu Asn
    990                 995                 1000

cgg gct gtc gat gag caa ggc tgg gag tat agc atc acc atc ccc ccg      3433
Arg Ala Val Asp Glu Gln Gly Trp Glu Tyr Ser Ile Thr Ile Pro Pro
1005                1010                1015                1020

gag cgg aag ccg aag cac tgg gtc cct gct gag aag atg tac tac aca      3481
Glu Arg Lys Pro Lys His Trp Val Pro Ala Glu Lys Met Tyr Tyr Thr
                1025                1030                1035

cac cga cgg cgg cgc tgg gtg cgc ctg cgc agg agg gat ctc agc caa      3529
His Arg Arg Arg Arg Trp Val Arg Leu Arg Arg Arg Asp Leu Ser Gln
            1040                1045                1050

atg gaa gca ctg aaa agg cac agg cag gcg gag gcg gag ggc gag ggc      3577
Met Glu Ala Leu Lys Arg His Arg Gln Ala Glu Ala Glu Gly Glu Gly
        1055                1060                1065

tgg gag tac gcc tct ctt ttt ggc tgg aag ttc cac ctc gag tac cgc      3625
Trp Glu Tyr Ala Ser Leu Phe Gly Trp Lys Phe His Leu Glu Tyr Arg
    1070                1075                1080

aag aca gat gcc ttc cgc cgc cgc cgc tgg cgc cgt cgc atg gag cca      3673
Lys Thr Asp Ala Phe Arg Arg Arg Arg Trp Arg Arg Arg Met Glu Pro
1085                1090                1095                1100

ctg gag aag acg ggg cct gca gct gtg ttt gcc ctt gag ggg gcc ctg      3721
Leu Glu Lys Thr Gly Pro Ala Ala Val Phe Ala Leu Glu Gly Ala Leu
                1105                1110                1115

ggc ggc gtg atg gat gac aag agt gaa gat tcc atg tcc gtc tcc acc      3769
Gly Gly Val Met Asp Asp Lys Ser Glu Asp Ser Met Ser Val Ser Thr
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ttg agc ttc ggt gtg aac aga ccc acg att tcc tgc ata ttc gac tat      3817
Leu Ser Phe Gly Val Asn Arg Pro Thr Ile Ser Cys Ile Phe Asp Tyr
        1135                1140                1145

ggg aac cgc tac cat cta cgc tgc tac atg tac cag gcc cgg gac ctg      3865
Gly Asn Arg Tyr His Leu Arg Cys Tyr Met Tyr Gln Ala Arg Asp Leu
    1150                1155                1160

gct gcg atg gac aag gac tct ttt tct gat ccc tat gcc atc gtc tcc      3913
Ala Ala Met Asp Lys Asp Ser Phe Ser Asp Pro Tyr Ala Ile Val Ser
1165                1170                1175                1180
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                1185                1190                1195

ccc acc tgg gac cag acg ctc atc ttc tac gag atc gag atc ttt ggc     4009
Pro Thr Trp Asp Gln Thr Leu Ile Phe Tyr Glu Ile Glu Ile Phe Gly
            1200                1205                1210

gag ccg gcc aca gtt gct gag caa ccg ccc agc att gtg gtg gag ctg     4057
Glu Pro Ala Thr Val Ala Glu Gln Pro Pro Ser Ile Val Val Glu Leu
        1215                1220                1225

tac gac cat gac act tat ggt gca gac gag ttt atg ggt cgc tgc atc     4105
Tyr Asp His Asp Thr Tyr Gly Ala Asp Glu Phe Met Gly Arg Cys Ile
    1230                1235                1240

tgt caa ccg agt ctg gaa cgg atg cca cgg ctg gcc tgg ttc cca ctg     4153
Cys Gln Pro Ser Leu Glu Arg Met Pro Arg Leu Ala Trp Phe Pro Leu
1245                1250                1255                1260

acg agg ggc agc cag ccg tcg ggg gag ctg ctg gcc tct ttt gag ctc     4201
Thr Arg Gly Ser Gln Pro Ser Gly Glu Leu Leu Ala Ser Phe Glu Leu
                1265                1270                1275

atc cag aga gag aag ccg gcc atc cac cat att cct ggt ttt gag gtg     4249
Ile Gln Arg Glu Lys Pro Ala Ile His His Ile Pro Gly Phe Glu Val
            1280                1285                1290

cag gag aca tca agg atc ctg gat gag tct gag gac aca gac ctg ccc     4297
Gln Glu Thr Ser Arg Ile Leu Asp Glu Ser Glu Asp Thr Asp Leu Pro
        1295                1300                1305

tac cca cca ccc cag agg gag gcc aac atc tac atg gtt cct cag aac     4345
Tyr Pro Pro Pro Gln Arg Glu Ala Asn Ile Tyr Met Val Pro Gln Asn
    1310                1315                1320

atc aag cca gcg ctc cag cgt acc gcc atc gag atc ctg gca tgg ggc     4393
Ile Lys Pro Ala Leu Gln Arg Thr Ala Ile Glu Ile Leu Ala Trp Gly
1325                1330                1335                1340

ctg cgg aac atg aag agt tac cag ctg gcc aac atc tcc tcc ccc agc     4441
Leu Arg Asn Met Lys Ser Tyr Gln Leu Ala Asn Ile Ser Ser Pro Ser
                1345                1350                1355

ctc gtg gta gag tgt ggg ggc cag acg gtg cag tcc tgt gtc atc agg     4489
Leu Val Val Glu Cys Gly Gly Gln Thr Val Gln Ser Cys Val Ile Arg
            1360                1365                1370

aac ctc cgg aag aac ccc aac ttt gac atc tgc acc ctc ttc atg gaa     4537
Asn Leu Arg Lys Asn Pro Asn Phe Asp Ile Cys Thr Leu Phe Met Glu
        1375                1380                1385

gtg atg ctg ccc agg gag gag ctc tac tgc ccc ccc atc acc gtc aag     4585
Val Met Leu Pro Arg Glu Glu Leu Tyr Cys Pro Pro Ile Thr Val Lys
    1390                1395                1400

gtc atc gat aac cgc cag ttt ggc cgc cgg cct gtg gtg ggc cag tgt     4633
Val Ile Asp Asn Arg Gln Phe Gly Arg Arg Pro Val Val Gly Gln Cys
1405                1410                1415                1420

acc atc cgc tcc ctg gag agc ttc ctg tgt gac ccc tac tcg gcg gag     4681
Thr Ile Arg Ser Leu Glu Ser Phe Leu Cys Asp Pro Tyr Ser Ala Glu
                1425                1430                1435

agt cca tcc cca cag ggt ggc cca gac gat gtg agc cta ctc agt cct     4729
Ser Pro Ser Pro Gln Gly Gly Pro Asp Asp Val Ser Leu Leu Ser Pro
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ggg gaa gac gtg ctc atc gac att gat gac aag gag ccc ctc atc ccc      4777
Gly Glu Asp Val Leu Ile Asp Ile Asp Asp Lys Glu Pro Leu Ile Pro
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atc cag gag gaa gag ttc atc gat tgg tgg agc aaa ttc ttt gcc tcc      4825
Ile Gln Glu Glu Glu Phe Ile Asp Trp Trp Ser Lys Phe Phe Ala Ser
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ata ggg gag agg gaa aag tgc ggc tcc tac ctg gag aag gat ttt gac      4873
Ile Gly Glu Arg Glu Lys Cys Gly Ser Tyr Leu Glu Lys Asp Phe Asp
1485                1490                1495                1500

acc ctg aag gtc tat gac aca cag ctg gag aat gtg gag gcc ttt gag      4921
Thr Leu Lys Val Tyr Asp Thr Gln Leu Glu Asn Val Glu Ala Phe Glu
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ggc ctg tct gac ttt tgt aac acc ttc aag ctg tac cgg ggc aag acg      4969
Gly Leu Ser Asp Phe Cys Asn Thr Phe Lys Leu Tyr Arg Gly Lys Thr
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cag gag gag aca gaa gat cca tct gtg att ggt gaa ttt aag ggc ctc      5017
Gln Glu Glu Thr Glu Asp Pro Ser Val Ile Gly Glu Phe Lys Gly Leu
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ttc aaa att tat ccc ctc cca gaa gac cca gcc atc ccc atg ccc cca      5065
Phe Lys Ile Tyr Pro Leu Pro Glu Asp Pro Ala Ile Pro Met Pro Pro
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Arg Gln Phe His Gln Leu Ala Ala Gln Gly Pro Gln Glu Cys Leu Val
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Arg Ile Tyr Ile Val Arg Ala Phe Gly Leu Gln Pro Lys Asp Pro Asn
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gga aag tgt gat cct tac atc aag atc tcc ata ggg aag aaa tca gtg      5209
Gly Lys Cys Asp Pro Tyr Ile Lys Ile Ser Ile Gly Lys Lys Ser Val
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agt gac cag gat aac tac atc ccc tgc acg ctg gag ccc gta ttt gga      5257
Ser Asp Gln Asp Asn Tyr Ile Pro Cys Thr Leu Glu Pro Val Phe Gly
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aag atg ttc gag ctg acc tgc act ctg cct ctg gag aag gac cta aag      5305
Lys Met Phe Glu Leu Thr Cys Thr Leu Pro Leu Glu Lys Asp Leu Lys
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atc act ctc tat gac tat gac ctc ctc tcc aag gac gaa aag atc ggt      5353
Ile Thr Leu Tyr Asp Tyr Asp Leu Leu Ser Lys Asp Glu Lys Ile Gly
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gag acg gtc gtc gac ctg gag aac agg ctg ctg tcc aag ttt ggg gct      5401
Glu Thr Val Val Asp Leu Glu Asn Arg Leu Leu Ser Lys Phe Gly Ala
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cgc tgt gga ctc cca cag acc tac tgt gtc tct gga ccg aac cag tgg      5449
Arg Cys Gly Leu Pro Gln Thr Tyr Cys Val Ser Gly Pro Asn Gln Trp
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cgg gac cag ctc cgc ccc tcc cag ctc ctc cac ctc ttc tgc cag cag      5497
Arg Asp Gln Leu Arg Pro Ser Gln Leu Leu His Leu Phe Cys Gln Gln
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His Arg Val Lys Ala Pro Val Tyr Arg Thr Asp Arg Val Met Phe Gln
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gat aaa gaa tat tcc att gaa gag ata gag gct ggc agg atc cca aac      5593
Asp Lys Glu Tyr Ser Ile Glu Glu Ile Glu Ala Gly Arg Ile Pro Asn
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cca cac ctg ggc cca gtg gag gag cgt ctg gct ctg cat gtg ctt cag      5641
Pro His Leu Gly Pro Val Glu Glu Arg Leu Ala Leu His Val Leu Gln
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cag cag ggc ctg gtc ccg gag cac gtg gag tca cgg ccc ctc tac agc      5689
Gln Gln Gly Leu Val Pro Glu His Val Glu Ser Arg Pro Leu Tyr Ser
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Pro Leu Gln Pro Asp Ile Glu Gln Gly Lys Leu Gln Met Trp Val Asp
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cta ttt ccg aag gcc ctg ggg cgg cct gga cct ccc ttc aac atc acc      5785
Leu Phe Pro Lys Ala Leu Gly Arg Pro Gly Pro Pro Phe Asn Ile Thr
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cca cgg aga gcc aga agg ttt ttc ctg cgt tgt att atc tgg aat acc      5833
Pro Arg Arg Ala Arg Arg Phe Phe Leu Arg Cys Ile Ile Trp Asn Thr
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aga gat gtg atc ctg gat gac ctg agc ctc acg ggg gag aag atg agc      5881
Arg Asp Val Ile Leu Asp Asp Leu Ser Leu Thr Gly Glu Lys Met Ser
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gac att tat gtg aaa ggt tgg atg att ggc ttt gaa gaa cac aag caa      5929
Asp Ile Tyr Val Lys Gly Trp Met Ile Gly Phe Glu Glu His Lys Gln
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aag aca gac gtg cat tat cgt tcc ctg gga ggt gaa ggc aac ttc aac      5977
Lys Thr Asp Val His Tyr Arg Ser Leu Gly Gly Glu Gly Asn Phe Asn
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tgg agg ttc att ttc ccc ttc gac tac ctg cca gct gag caa gtc tgt      6025
Trp Arg Phe Ile Phe Pro Phe Asp Tyr Leu Pro Ala Glu Gln Val Cys
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acc att gcc aag aag gat gcc ttc tgg agg ctg gac aag act gag agc      6073
Thr Ile Ala Lys Lys Asp Ala Phe Trp Arg Leu Asp Lys Thr Glu Ser
1885                1890                1895                1900

aaa atc cca gca cga gtg gtg ttc cag atc tgg gac aat gac aag ttc      6121
Lys Ile Pro Ala Arg Val Val Phe Gln Ile Trp Asp Asn Asp Lys Phe
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tcc ttt gat gat ttt ctg ggc tcc ctg cag ctc gat ctc aac cgc atg      6169
Ser Phe Asp Asp Phe Leu Gly Ser Leu Gln Leu Asp Leu Asn Arg Met
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ccc aag cca gcc aag aca gcc aag aag tgc tcc ttg gac cag ctg gat      6217
Pro Lys Pro Ala Lys Thr Ala Lys Lys Cys Ser Leu Asp Gln Leu Asp
        1935                1940                1945

gat gct ttc cac cca gaa tgg ttt gtg tcc ctt ttt gag cag aaa aca      6265
Asp Ala Phe His Pro Glu Trp Phe Val Ser Leu Phe Glu Gln Lys Thr
    1950                1955                1960

gtg aag ggc tgg tgg ccc tgt gta gca gaa gag ggt gag aag aaa ata      6313
Val Lys Gly Trp Trp Pro Cys Val Ala Glu Glu Gly Glu Lys Lys Ile
1965                1970                1975                1980
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ctg gcg ggc aag ctg gaa atg acc ttg gag att gta gca gag agt gag      6361
Leu Ala Gly Lys Leu Glu Met Thr Leu Glu Ile Val Ala Glu Ser Glu
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cat gag gag cgg cct gct ggc cag ggc cgg gat gag ccc aac atg aac      6409
His Glu Glu Arg Pro Ala Gly Gln Gly Arg Asp Glu Pro Asn Met Asn
            2000                2005                2010

cct aag ctt gag gac cca agg cgc ccc gac acc tcc ttc ctg tgg ttt      6457
Pro Lys Leu Glu Asp Pro Arg Arg Pro Asp Thr Ser Phe Leu Trp Phe
        2015                2020                2025

acc tcc cca tac aag acc atg aag ttc atc ctg tgg cgg cgt ttc cgg      6505
Thr Ser Pro Tyr Lys Thr Met Lys Phe Ile Leu Trp Arg Arg Phe Arg
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tgg gcc atc atc ctc ttc atc atc ctc ttc atc ctg ctg ctg ttc ctg      6553
Trp Ala Ile Ile Leu Phe Ile Ile Leu Phe Ile Leu Leu Leu Phe Leu
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gcc atc ttc atc tac gcc ttc ccg aac tat gct gcc atg aag ctg gtg      6601
Ala Ile Phe Ile Tyr Ala Phe Pro Asn Tyr Ala Ala Met Lys Leu Val
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Lys Pro Phe Ser
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Gly Phe Glu Trp Asp Leu Lys Gly Ile Pro Leu Asp Gln Gly Ser Glu
     50                  55                  60
Leu His Val Val Val Lys Asp His Glu Thr Met Gly Arg Asn Arg Phe
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Leu Gly Glu Ala Lys Val Pro Leu Arg Glu Val Leu Ala Thr Pro Ser
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Leu Ser Ala Ser Phe Asn Ala Pro Leu Leu Asp Thr Lys Lys Gln Pro
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Thr Gly Ala Ser Leu Val Leu Gln Val Ser Tyr Thr Pro Leu Pro Gly
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Ala Val Pro Leu Phe Pro Pro Pro Thr Pro Leu Glu Pro Ser Pro Thr
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Glu Asp Gln Gly Leu Thr Gly Asp Glu Ala Glu Pro Phe Leu Asp Gln
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<400> 30
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<210> 31
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<211> 264
<212> DNA
<213> Homo sapiens

<400> 33
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<210> 34
<211> 223
<212> DNA
<213> Homo sapiens

<400> 34
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gcttcaatgc ccccctgctg gacaccaaga agcagcccac aggggtaagt gcccatcagc 180
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<210> 35
<211> 224
<212> DNA
<213> Homo sapiens

<400> 35
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<210> 36
<211> 315
<212> DNA
<213> Homo sapiens

<400> 36
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ccatcagctg cgggt 315

<210> 37
<211> 249
<212> DNA
<213> Homo sapiens

<400> 37
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accttgtgg 249

<210> 38
<211> 185
<212> DNA
<213> Homo sapiens

<400> 38
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cacac 185

<210> 39
<211> 196
<212> DNA
<213> Homo sapiens

<400> 39
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taattgctta ttttctaaaa gcagtcagtt ctcacttctc cgtgttggtg gagcctctgt 180
ggaccatggg cagggg 196

<210> 40
<211> 178
<212> DNA
<213> Homo sapiens

<400> 40
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tctcctctct tgattgcaga tggacgtggg caccatttac agagagcccc gtgagttctc 120
accactttgg ccgtatcctt gcattttggt tctggaggct gattggggac actcattt 178

<210> 41
<211> 231
<212> DNA
<213> Homo sapiens

<400> 41
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aaaacaagcc tttgtgtgct ggggcctggg gacgaagcgc ctgtgagtac atttccctgg 180
gtcttcctta cggtccccca cgcggcactt ggttgcggag gcaccaaacc a 231

<210> 42
<211> 247
<212> DNA
<213> Homo sapiens

<400> 42
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gagaaaagac ccctctgaag acaaggagga cattgaaagc aacctgctcc ggcccacagg 120
cgtagccctg cgaggagccc acttctgcct gaaggtcttc cgggccgagg acttgccgca 180
gagtgcgtgg ggcgcgccct tgggtgggag gtctgcagga ggctggaggc gcagggctgg 240
tgggggt 247

<210> 43
<211> 179
<212> DNA
<213> Homo sapiens

<400> 43
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tttgcgggga aaatggtaag gagcaaggga gcaggagggt tctctcggga ggggacggg 179

<210> 44
<211> 202
<212> DNA
<213> Homo sapiens

<400> 44
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tgcctgccat ggtgagcctc ctgtccccag caaacccaag gaggcccctg gggctctggg 180
cttcgggagg tccagggctc ct 202

<210> 45
<211> 167
<212> DNA
<213> Homo sapiens

<400> 45
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agtttccctc catgtgcgaa aaaatgagga ttcgtatcat agactggtga gttctgagtc 120
ttggagtctt tagggcgggc tgtcctgagg gggcgctccc tcagttt 167

<210> 46
<211> 220
<212> DNA
<213> Homo sapiens

<400> 46
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cctgactcac aatgacatcg tggctaccac ctacctgagt atgtcgaaaa tctctgcccc 120
tggaggagaa atagaaggta tgttccctct tcgttctgcc ctttgacccc ctgtgctctc 180
ccccccctcta tccagcttac acttctagtt ttgagagttt 220

<210> 47
<211> 172
<212> DNA
<213> Homo sapiens

<400> 47
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ttctttacgc ttcagaggag cctgcaggtg ctgtcaagcc ttcgaaagcc tcagactgta 120
cgttgctgtc accttgggga caaccagggg agtggggcct tgggttttgg ct 172

<210> 48
<211> 200
<212> DNA
<213> Homo sapiens

<400> 48
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acccctacac agagctcaac acaggcaagg taagccggct ggagccctgg caagggcagg 180
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<210> 49
<211> 217
<212> DNA
<213> Homo sapiens

<400> 49
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aggtggagga ccttcctgcg gatgacatcc tccgggtgga ggtgaggggt gtggctctgg 180

gtgggagctg ggcgtcgggg cagggaaggg atggcca 217

<210> 50
<211> 269
<212> DNA
<213> Homo sapiens

<400> 50
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ggcagtgctc ctggctggga ccccgatca 269

<210> 51
<211> 225
<212> DNA
<213> Homo sapiens

<400> 51
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ccaaagctgc acatgcctat gcatgcacct gctacccccg ctgca 225

<210> 52
<211> 227
<212> DNA
<213> Homo sapiens

<400> 52
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gtggactcgc tggtggctca gctgacggat gagctcatcg caggctgcag gtaggggga 180
cctggcgccc ctggtgccca cctctcctgg ctcaactggg cctgttt 227

<210> 53
<211> 303
<212> DNA
<213> Homo sapiens

<400> 53
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aac 303

<210> 54
<211> 272
<212> DNA
<213> Homo sapiens

<400> 54
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tccaacataa ggcctttctc ccatctcttg ct 272

<210> 55
<211> 219
<212> DNA
<213> Homo sapiens

<400> 55
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aaccagtttg ctgaggggaa gctgtctgtc tttgctgaaa ccgtgagtac ctgccagccc 180
ccacctctgc ctcccactac ctggagctgc cttggcccc 219

<210> 56
<211> 292
<212> DNA
<213> Homo sapiens

<400> 56
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<210> 57
<211> 242
<212> DNA
<213> Homo sapiens

<400> 57
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ca 242

<210> 58
<211> 215
<212> DNA
<213> Homo sapiens

<400> 58
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aaggtgcttc ccaaggatga cattgagtgc ccactgggct ggaagtggga agatgaggaa 120
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gagccccatc cccggcaagc tctcaagcca tgcat 215

<210> 59
<211> 246
<212> DNA
<213> Homo sapiens

<400> 59
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gcctgt 246

<210> 60
<211> 253
<212> DNA
<213> Homo sapiens

<400> 60
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ctgcagctgt gtttgccctt gaggggggccc tggtatgtgg ggctgcactt gtcctggctt 240
gggtagggta tat 253

<210> 61
<211> 177

<212> DNA
<213> Homo sapiens

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ttccatgtcc gtctccacct tgagcttcgg tgtgaacaga cccacgattt cctgcatatt 120
cgactgtaag taggcttcga ggcctctatg gggtgataag ggtgtgtcac cttatgc 177

<210> 62
<211> 181
<212> DNA
<213> Homo sapiens

<400> 62
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tttttctggt aggtgggaga gaggcaggag agtcagagac tgtgggctga gatctgggaa 180
t 181

<210> 63
<211> 319
<212> DNA
<213> Homo sapiens

<400> 63
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accatgtgca aaggtgggg 319

<210> 64
<211> 249
<212> DNA
<213> Homo sapiens

<400> 64
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ggccaaccc 249

<210> 65
<211> 158
<212> DNA
<213> Homo sapiens

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gtcttgctct gacctttcct tcttcaaact gattgcca 158

<210> 66
<211> 132
<212> DNA
<213> Homo sapiens

<400> 66
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caggtgcagg agacatcaag gatcctggat gaggtgagct ggcggggccg aggtagaggg 120
aaggtgaagc ca 132

<210> 67
<211> 216
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<213> Homo sapiens

<400> 67
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agcagcctgc ccttcccctt cctggcccca gccttt 216

<210> 68
<211> 263
<212> DNA
<213> Homo sapiens

<400> 68
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<210> 69
<211> 249
<212> DNA
<213> Homo sapiens

<400> 69
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<210> 70
<211> 180
<212> DNA
<213> Homo sapiens

<400> 70
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<210> 71
<211> 211
<212> DNA
<213> Homo sapiens

<400> 71
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ggtgtgtgtg tgcgtgctgg gcagtgggag a 211

<210> 72
<211> 235
<212> DNA
<213> Homo sapiens

<400> 72
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acacacagct ggagaatgtg gaggcctttg agggcctgtc tgacttttgt aacaccttca 120
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aggtaaatcc tcgaagacgt ccctaaccca ggtgggccta agactgtggt gttgg 235

<210> 73
<211> 268
<212> DNA

<213> Homo sapiens

<400> 73
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<210> 74
<211> 200
<212> DNA
<213> Homo sapiens

<400> 74
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ataacccaca gtctagtggg 200

<210> 75
<211> 263
<212> DNA
<213> Homo sapiens

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<212> DNA
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gggagttcat ca 252

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35 40 45
Phe Leu Gly
50

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Thr Leu Pro Ala Met Phe Pro Ser Met Cys Glu Lys Met Arg Ile Arg
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Ile Ile Asp Trp Asp Arg Leu Thr His Asn Asp Ile Val
35 40 45

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35 40 45
Ile Glu Ile Phe Gly Glu Pro Ala Thr Val Ala Glu Gln Pro Pro Ser
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Met Gly

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35 40 45
Met Phe Glu Leu Thr Cys Thr Leu Pro Leu Glu Lys Asp Leu Lys Ile
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gt 62

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Leu Gly Arg Leu Ser Leu Glu Lys Gly Arg Phe Val Asn Pro Gly Gly
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aga ggt aga gat cca gga gag ggc ggc gtg atg gat gac aag agt gaa      516
Arg Gly Arg Asp Pro Gly Glu Gly Gly Val Met Asp Asp Lys Ser Glu
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gat tcc atg tcc gtc tcc acc ttg agc ttc ggt gtg aac aga ccc acg      564
Asp Ser Met Ser Val Ser Thr Leu Ser Phe Gly Val Asn Arg Pro Thr
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att tcc tgc ata ttc gac tat ggg aac cgc tac cat cta cgc tgc tac      612
Ile Ser Cys Ile Phe Asp Tyr Gly Asn Arg Tyr His Leu Arg Cys Tyr
    50                  55                  60                  65

atg tac cag gcc cgg gac ctg gct gcg atg gac aag gac tct ttt tct      660
Met Tyr Gln Ala Arg Asp Leu Ala Ala Met Asp Lys Asp Ser Phe Ser
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gat ccc tat gcc atc gtc tcc ttc ctg cac cag agc cag aag acg gtg      708
Asp Pro Tyr Ala Ile Val Ser Phe Leu His Gln Ser Gln Lys Thr Val
            85                  90                  95

gtg gtg aag aac acc ctt aac ccc acc tgg gac cag acg ctc atc ttc      756
Val Val Lys Asn Thr Leu Asn Pro Thr Trp Asp Gln Thr Leu Ile Phe
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Tyr Glu Ile Glu Ile Phe Gly Glu Pro Ala Thr Val Ala Glu Gln Pro
    115                 120                 125

ccc agc att gtg gtg gag ctg tac gac cat gac act tat ggt gca gac      852
Pro Ser Ile Val Val Glu Leu Tyr Asp His Asp Thr Tyr Gly Ala Asp
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gag ttt atg ggt cgc tgc atc tgt caa ccg agt ctg gaa cgg atg cca      900
Glu Phe Met Gly Arg Cys Ile Cys Gln Pro Ser Leu Glu Arg Met Pro
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cgg ctg gcc tgg ttc cca ctg acg agg ggc agc cag ccg tcg ggg gag      948
Arg Leu Ala Trp Phe Pro Leu Thr Arg Gly Ser Gln Pro Ser Gly Glu
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ctg ctg gcc tct ttt gag ctc atc cag aga gag aag ccg gcc atc cac      996
Leu Leu Ala Ser Phe Glu Leu Ile Gln Arg Glu Lys Pro Ala Ile His
        180                 185                 190

cat att cct ggt ttt gag gtg cag gag aca tca agg atc ctg gat gag     1044
His Ile Pro Gly Phe Glu Val Gln Glu Thr Ser Arg Ile Leu Asp Glu
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tct gag gac aca gac ctg ccc tac cca cca ccc cag agg gag gcc aac     1092
Ser Glu Asp Thr Asp Leu Pro Tyr Pro Pro Pro Gln Arg Glu Ala Asn
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atc tac atg gtt cct cag aac atc aag cca gcg ctc cag cgt acc gcc     1140
Ile Tyr Met Val Pro Gln Asn Ile Lys Pro Ala Leu Gln Arg Thr Ala
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gcc aac atc tcc tcc ccc agc ctc gtg gta gag tgt ggg ggc cag acg      1236
Ala Asn Ile Ser Ser Pro Ser Leu Val Val Glu Cys Gly Gly Gln Thr
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gtg cag tcc tgt gtc atc agg aac ctc cgg aag aac ccc aac ttt gac      1284
Val Gln Ser Cys Val Ile Arg Asn Leu Arg Lys Asn Pro Asn Phe Asp
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atc tgc acc ctc ttc atg gaa gtg atg ctg ccc agg gag gag ctc tac      1332
Ile Cys Thr Leu Phe Met Glu Val Met Leu Pro Arg Glu Glu Leu Tyr
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tgc ccc ccc atc acc gtc aag gtc atc gat aac cgc cag ttt ggc cgc      1380
Cys Pro Pro Ile Thr Val Lys Val Ile Asp Asn Arg Gln Phe Gly Arg
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cgg cct gtg gtg ggc cag tgt acc atc cgc tcc ctg gag agc ttc ctg      1428
Arg Pro Val Val Gly Gln Cys Thr Ile Arg Ser Leu Glu Ser Phe Leu
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tgt gac ccc tac tcg gcg gag agt cca tcc cca cag ggt ggc cca gac      1476
Cys Asp Pro Tyr Ser Ala Glu Ser Pro Ser Pro Gln Gly Gly Pro Asp
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gat gtg agc cta ctc agt cct ggg gaa gac gtg ctc atc gac att gat      1524
Asp Val Ser Leu Leu Ser Pro Gly Glu Asp Val Leu Ile Asp Ile Asp
    355                 360                 365

gac aag gag ccc ctc atc ccc atc cag gag gaa gag ttc atc gat tgg      1572
Asp Lys Glu Pro Leu Ile Pro Ile Gln Glu Glu Glu Phe Ile Asp Trp
370                 375                 380                 385

tgg agc aaa ttc ttt gcc tcc ata ggg gag agg gaa aag tgc ggc tcc      1620
Trp Ser Lys Phe Phe Ala Ser Ile Gly Glu Arg Glu Lys Cys Gly Ser
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tac ctg gag aag gat ttt gac acc ctg aag gtc tat gac aca cag ctg      1668
Tyr Leu Glu Lys Asp Phe Asp Thr Leu Lys Val Tyr Asp Thr Gln Leu
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gag aat gtg gag gcc ttt gag ggc ctg tct gac ttt tgt aac acc ttc      1716
Glu Asn Val Glu Ala Phe Glu Gly Leu Ser Asp Phe Cys Asn Thr Phe
        420                 425                 430

aag ctg tac cgg ggc aag acg cag gag gag aca gaa gat cca tct gtg      1764
Lys Leu Tyr Arg Gly Lys Thr Gln Glu Glu Thr Glu Asp Pro Ser Val
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att ggt gaa ttt aag ggc ctc ttc aaa att tat ccc ctc cca gaa gac      1812
Ile Gly Glu Phe Lys Gly Leu Phe Lys Ile Tyr Pro Leu Pro Glu Asp
450                 455                 460                 465

cca gcc atc ccc atg ccc cca aga cag ttc cac cag ctg gcc gcc cag      1860
Pro Ala Ile Pro Met Pro Pro Arg Gln Phe His Gln Leu Ala Ala Gln
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gga ccc cag gag tgc ttg gtc cgt atc tac att gtc cga gca ttt ggc      1908
Gly Pro Gln Glu Cys Leu Val Arg Ile Tyr Ile Val Arg Ala Phe Gly
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ctg cag ccc aag gac ccc aat gga aag tgt gat cct tac atc aag atc      1956
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acg ctg gag ccc gta ttt gga aag atg ttc gag ctg acc tgc act ctg      2052
Thr Leu Glu Pro Val Phe Gly Lys Met Phe Glu Leu Thr Cys Thr Leu
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cct ctg gag aag gac cta aag atc act ctc tat gac tat gac ctc ctc      2100
Pro Leu Glu Lys Asp Leu Lys Ile Thr Leu Tyr Asp Tyr Asp Leu Leu
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tcc aag gac gaa aag atc ggt gag acg gtc gtc gac ctg gag aac agg      2148
Ser Lys Asp Glu Lys Ile Gly Glu Thr Val Val Asp Leu Glu Asn Arg
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85 90 95
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19395

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C12N 15/11, 15/00; C07K 16/00
US CL : 536/23.1, 435/440, 530/387.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 435/440, 530/387.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

BIOSIS, CAPLUS, EMBASE, ESBIOBASE, LIFESCI, MEDLINE, SCISEARCH, TOXLIT
Search Terms: dysferlin, lgmd2b

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WEILER et al. Limb-girdle muscular dystrophy and Myoshi Myopathy in an aboriginal Canadian kindred map to LGMD2B and segregate with the same haplotype. American Journal of Human Genetics. October 1996, Vol.59, pages 872-878, especially page 873.	32,35
X	KOENIG et al. Complete cloning of the Duchenne Muscular Dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. Cell. 31 July 1987, Vol. 50, pages 509-517, especially pages 511-513.	32-33,36

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

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"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 NOVEMBER 1999	Date of mailing of the international search report 13 JAN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-4242	Authorized officer Stephen Siu Telephone No. (703) 308-0196

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19395

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P --- Y,P	Database GenCore version 4.5, Compugen Ltd., No. AI128455, 'NCI-CGAP, National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index', Unpublished, 27 October 1998	1,6,12 ----- 7,14,16
X --- Y	Database GenCore version 4.5, Compugen Ltd., No. R41062, WAYE, M.M.Y. et al. 'Gene expression of adult human heart as revealed by random sequencing of cDNA library,' Miami Winter Biotechnol. Symp. Proc. 6,90 , 16 May 16, 1995.	1, 6, 11-12 ----- 7, 14
X --- Y	Database GenCore version 4.5, Compugen Ltd., No. AA718275, Marra et al, 'The WashU-HHMI Mouse EST Project', Unpublished, 29 December 1997.	1, 6, 11-12 ---------- 7, 14
Y	BASHIR et al. Genetic and physical mapping at the limb-girdle muscular dystrophy locus (LGMD2B) on chromosome 2p. Genomics. April 1996, Vol.33, pages 46-52, especially page 47.	32,36
Y	MOREIRA et al. The seventh form of autosomal recessive limb-girdle muscular dystrophy is mapped to 17q11-12. American Journal of Human Genetics. July 1997, Vol. 61, pages 151-159, entire document.	32, 35
Y	Database GenCore version 4.5, Compugen Ltd., No. R76778, HILLIER et al., 'The WashU-Merck EST Project', Unpublished, 06 June 1995.	7, 14
A,E	AHLBERG et al. Genetic Linkage of Welander Distal Myopathy to chromosome 2p13. Annals of Neurology. September 1999, Vol. 46, No.3, pages 399-404, especially page 400.	37, 39
A,E	BITTNER et al. Dysferlin deletion in SJL mice (SJL-Dysf) defines a natural model for limb girdle muscular dystrophy 2B. Nature Genetics. October 1999, Vol. 23, pages 141-142, especially page 141.	40
A,P	BASHIR et al. A gene related to Caenorhabditis elegans spermatogenesis factor fer-1 is mutated in limb-girdle muscular dystrophy type 2B. Nature Genetics. September 1998, Vol 20, pages 37-42.	1-53
A,E	Matsuda et al. Dysferlin is a surface membrane-associated protein that is absent in Miyoshi Myopathy. Neurology 22 September 1999, Vol. 53, No. 5, pages 1119-1122, especially pages 1119-1120.	40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19395

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	LIU et al. Dysferlin, a novel skeletal muscle gene, is mutated in Miyoshi Myopathy and limb girdle muscular dystrophy. Nature Genetics. September 1998, Vol. 20, pages 31-36.	1-54

CORRECTED VERSION*

PCT

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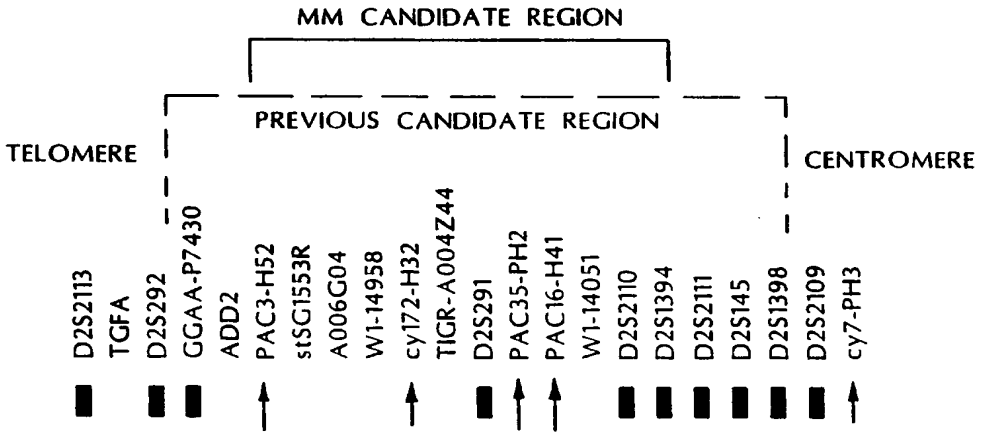
(54) Title: DYSFERLIN, A GENE MUTATED IN DISTAL MYOPATHY AND LIMB GIRDLE MUSCULAR DYSTROPHY



(57) Abstract

A novel gene and the protein encoded therein, i.e., dysferlin, are disclosed. This gene and its expression products are associated with muscular dystrophy, e.g., Miyoshi myopathy and limb girdle muscular dystrophy 2B.

*(Referred to in PCT Gazette No. 33/2000, Section II)

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DYSFERLIN, A GENE MUTATED IN DISTAL MYOPATHY AND LIMB GIRDLE MUSCULAR DYSTROPHY

RELATED APPLICATION INFORMATION

This application claims priority from provisional application serial no. 60/097,927, filed August 25, 1998.

Statement as to Federally Sponsored Research

The work described herein was supported in part by NIH grants 5P01AG12992, 5R01N834913A, and 5P01NS31248. The Federal Government therefore may have certain rights in the invention.

Background of the Invention

The invention relates to genes involved in the onset of muscular dystrophy.

Muscular dystrophies constitute a heterogeneous group of disorders. Most are characterized by weakness and atrophy of the proximal muscles, although in rare myopathies such as "Miyoshi myopathy" symptoms may first arise in distal muscles. Of the various hereditary types of muscular dystrophy, several are caused by mutations or deletions in genes encoding individual components of the dystrophin-associated protein (DAP) complex. It is this DAP complex that links the cytoskeletal protein dystrophin to the extracellular matrix protein, laminin-2.

Muscular dystrophies may be classified according to the gene mutations that are associated with specific clinical syndromes. For example, mutations in the gene encoding the cytoskeletal protein dystrophin result in either Duchenne's Muscular Dystrophy or Becker's Muscular Dystrophy, whereas mutations in the gene encoding the extracellular matrix protein merosin produce Congenital

Muscular Dystrophy. Muscular dystrophies with an autosomal recessive mode of inheritance include "Miyoshi myopathy" and the several limb-girdle muscular dystrophies (LGMD2). Of the limb-girdle muscular dystrophies, the deficiencies resulting in LGMD2C, D, E, and F result from mutations in genes encoding the membrane-associated sarcoglycan components of the DAP complex.

Summary of the Invention

A novel protein, designated dysferlin, is identified and characterized. The dysferlin gene is normally expressed in skeletal muscle cells and is selectively mutated in several families with the hereditary muscular dystrophies, *e.g.*, Miyoshi myopathy (MM) and limb girdle muscular dystrophy-2B (LGMD2B). These characteristics of dysferlin render it a candidate disease gene for both MM and LGMD2B. An additional novel protein, brain-specific dysferlin, has also been identified. Defects in brain-specific dysferlin may predispose to selected disorders of the central nervous system. Moreover, the expression of brain-specific dysferlin may be important as a marker for normal neural development (e.g., *in vivo* or in neural cells in culture). Manipulation of levels of expression of brain-specific dysferlin, and of the type of expressed brain-specific dysferlin is of use for analyzing the function of brain-specific dysferlin and related dysferlin-associated molecules.

The invention features an isolated DNA which includes a nucleotide sequence hybridizing under stringent hybridization conditions to a strand of SEQ ID NO:3 or SEQ ID NO:117.

The invention also features an isolated DNA including a nucleotide sequence selected from SEQ ID NOs:4-12.

Also within the invention is an isolated DNA comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:22-30.

Also within the invention is a single stranded oligonucleotide of 14-50 nucleotides in length having a nucleotide sequence identical to a portion of a strand of SEQ ID NO:3.

Also within the invention is a pair of PCR primers consisting of:

(a) a first single stranded oligonucleotide consisting of 14-50 contiguous nucleotides of the sense strand of SEQ ID NO:117; and

(b) a second single stranded oligonucleotide consisting of 14-50 contiguous nucleotides of the antisense strand of SEQ ID NO:117, wherein the sequence of at least one of the oligonucleotides is identical to a portion of a strand of SEQ ID NO:3, and the first oligonucleotide is not complementary to the second oligonucleotide.

Also within the invention is a pair of single stranded oligonucleotides selected from of SEQ ID NOs 130-231, SEQ ID NO:110, and SEQ ID NO:112.

Also within the invention is an isolated DNA including a nucleotide sequence that encodes a protein that shares at least 70% sequence identity with SEQ ID NO:2, or a complement of the nucleotide sequence.

Also within the invention is an isolated DNA including a nucleotide sequence which hybridizes under stringent hybridization conditions to a strand of a nucleic acid, the nucleic acid having a sequence selected from SEQ ID NOs:31-79 and 90-101.

Also within the invention is a single stranded oligonucleotide of 14-50 nucleotides in length having a nucleotide sequence which is identical to a portion of a strand of a nucleic acid selected from SEQ ID NOs:31-79 and 90-100.

Also within the invention is a pair of PCR primers consisting of:

(a) a first single stranded oligonucleotide consisting of 14-50 contiguous nucleotides of the sense strand of a nucleic acid selected from SEQ ID NOs:31-85; and

(b) a second single stranded oligonucleotide consisting of 14-50 contiguous nucleotides of the antisense strand of a nucleic acid selected from SEQ ID NOs:31-85, wherein the sequence of at least one of the oligonucleotides includes a sequence identical to a portion of a strand of a nucleic acid selected from SEQ ID NOs: 31-79 and 90-100, and the first oligonucleotide is not complementary to the second oligonucleotide.

Also within the invention is a pair of single stranded oligonucleotides selected from SEQ ID NOs 101-116, SEQ ID NOs 184-185, SEQ ID NOs 188-191, SEQ ID NOs 210-213, and SEQ ID NOs 216-217.

Also within the invention is a substantially pure protein that has an amino acid sequence sharing at least 70% sequence identity with SEQ ID NO:2.

Also within the invention is a substantially pure protein the sequence of which includes amino acid residues 1-500, 501-1000, 1001-1500, or 1501-2080 of SEQ ID NO:2.

Also within the invention is a substantially pure protein including the amino acid sequence of SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88, or SEQ ID NO:89.

In another aspect, the invention features a transgenic non-human mammal having a transgene disrupting

or interfering with the expression of a dysferlin gene, the transgene being chromosomally integrated into the germ cells of the animal.

Another embodiment of the invention features a method of decreasing the symptoms of muscular dystrophy in a mammal by introducing into a cell of the mammal (e.g., a muscle cell or a muscle precursor cell) an isolated DNA which hybridizes under stringent hybridization conditions to a strand of SEQ ID NO:3.

Another aspect of the invention provides a method for identifying a patient, a fetus, or a pre-embryo at risk for having a dysferlin-related disorder by (a) providing a sample of genomic DNA from the patient, fetus, or pre-embryo; and (b) determining whether the sample contains a mutation in a dysferlin gene.

In another aspect, the invention provides a method for identifying a patient, a fetus, or a pre-embryo at risk for having a dysferlin-related disorder by (a) providing a sample including dysferlin mRNA from the patient, fetus, or pre-embryo; and (b) determining whether the dysferlin mRNA contains a mutation.

Methods of identifying mutations in a dysferlin sequence are useful for predicting (e.g., predicting whether an individual is at risk for developing a dysferlin-related disorder) or diagnosing disorders associated with dysferlin, e.g., MM and LGMD2B. Such methods can also be used to determine if an individual, fetus, or a pre-embryo is a carrier of a dysferlin mutation, for example in screening procedures. Methods which distinguish between different dysferlin alleles (e.g., a mutant dysferlin allele and a normal dysferlin allele) can be used to determine carrier status.

The invention also features an isolated nucleic acid comprising a nucleotide sequence which hybridizes under stringent hybridization conditions to nucleic acids

3284-3720 of SEQ ID NO:232, or the complement of the nucleotide sequence. An isolated nucleic acid including a nucleotide sequence identical to the sequence of nucleotides 3284-3720 of SEQ ID NO:232, or a complement of the nucleotide sequence is also a feature of the invention. The isolated nucleic acid can include the entire sequence of SEQ ID NO:232 or the complement of SEQ ID NO:232.

Another aspect of the invention features an isolated polypeptide that includes: a) at least 15 contiguous amino acids of the polypeptide comprising amino acids 1-24 of SEQ ID NO:233, b) a naturally occuring allelic variant of a polypeptide comprising amino acids 1-24 of SEQ ID NO:233, or c) an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes under stringent conditions to nucleotides 3284-3720 of SEQ ID NO:232. The polypeptide of this aspect can include the entire sequence of SEQ ID NO:233.

Also included in the invention is a vector comprising the nucleic acid of claim 44 and a cell that contains the vector. Another aspect of the invention features a method of making a polypeptide by culturing the cell which contains the vector.

The invention also features an antibody which specifically binds to a polypeptide of such as those described above. The antibody can bind to a polypeptide selected from amino acids 253-403 of SEQ ID NO:233, amino acids 624-865 of SEQ ID NO:233, and amino acids 1664-1786 of SEQ ID NO:233. Antibodies of the invention can be monclonal or polyclonal antibodies.

An "isolated DNA" is DNA which has a naturally occurring sequence corresponding to part or all of a given gene but is free of the two genes that normally flank the given gene in the genome of the organism in

which the given gene naturally occurs. The term therefore includes a recombinant DNA incorporated into a vector, into an autonomously replicating plasmid or virus, or into the genomic DNA of a prokaryote or eukaryote. It also includes a separate molecule such as a cDNA, a genomic fragment, a fragment produced by polymerase chain reaction (PCR), or a restriction fragment, as well as a recombinant nucleotide sequence that is part of a hybrid gene, i.e., a gene encoding a fusion protein. The term excludes intact chromosomes and large genomic segments containing multiple genes contained in vectors or constructs such as cosmids, yeast artificial chromosomes (YACs), and P1-derived artificial chromosome (PAC) contigs.

A "noncoding sequence" is a sequence which corresponds to part or all of an intron of a gene, or to a sequence which is 5′ or 3′ to a coding sequence and so is not normally translated.

An expression control sequence is "operably linked" to a coding sequence when it is within the same nucleic acid and can control expression of the coding sequence.

A "protein" or "polypeptide" is any chain of amino acids linked by peptide bonds, regardless of length or post-translational modification, e.g., glycosylation or phosphorylation.

As used herein, the term "percent sequence identity" means the percentage of identical subunits at corresponding positions in two sequences when the two sequences are aligned to maximize subunit matching, i.e., taking into account gaps and insertions. For purposes of the present invention, percent sequence identity between two polypeptides is to be determined using the Gap program and the default parameters as specified therein. The Gap program is part of the Sequence Analysis Software

Package of the Genetics Computer Group, University of Wisconsin Biotechnology Center, 1710 University Avenue, Madison, WI 53705.

The algorithm of Myers and Miller, CABIOS (1989) can also be used to determine whether two sequences are similar or identical. Such an algorithm is incorporated into the ALIGN program (version 2.0) which is part of the GCG sequence alignment software package. When utilizing the ALIGN program for comparing amino acid sequences, a PAM120 weight residue table, a gap length penalty of 12, and a gap penalty of 4 can be used.

As used herein, the term "stringent hybridization conditions" means the following DNA hybridization and wash conditions: hybridization at 60°C in the presence of 6 x SSC, 0.5% SDS, 5 x Denhardt's Reagent, and 100 μg/ml denatured salmon sperm DNA; followed by a first wash at room temperature for 20 minutes in 0.5 x SSC and 0.1% SDS and a second wash at 55°C for 30 minutes in 0.2 x SSC and 0.1% SDS.

A "substantially pure protein" is a protein separated from components that naturally accompany it. The protein is considered to be substantially pure when it is at least 60%, by dry weight, free from the proteins and other naturally-occurring organic molecules with which it is naturally associated. Preferably, the purity of the preparation is at least 75%, more preferably at least 90%, and most preferably at least 99%, by weight. A substantially pure dysferlin protein can be obtained, for example, by extraction from a natural source, by expression of a recombinant nucleic acid encoding a dysferlin polypeptide, or by chemical synthesis. Purity can be measured by any appropriate method, e.g., column chromatography, polyacrylamide gel electrophoresis, or HPLC analysis. A chemically synthesized protein or a recombinant protein produced in a cell type other than

the cell type in which it naturally occurs is, by definition, substantially free from components that naturally accompany it. Accordingly, substantially pure proteins include those having sequences derived from eukaryotic organisms but which have been recombinantly produced in *E. coli* or other prokaryotes.

An antibody that "specifically binds" to an antigen is an antibody that recognizes and binds to the antigen, e.g., a dysferlin polypeptide, but which does not substantially recognize and bind to other molecules in a sample (e.g., a biological sample) which naturally includes the antigen, e.g., a dysferlin polypeptide. An antibody that "specifically binds" to dysferlin is sufficient to detect a dysferlin polypeptide in a biological sample using one or more standard immunological techniques (for example, Western blotting or immunoprecipitation).

A "transgene" is any piece of DNA, other than an intact chromosome, which is inserted by artifice into a cell, and becomes part of the genome of the organism which develops from that cell. Such a transgene may include a gene which is partly or entirely heterologous (i.e., foreign) to the host organism, or may represent a gene homologous to an endogenous gene of the organism.

Unless otherwise defined, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Methods and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention. The present materials, methods, and examples are illustrative only and not intended to be limiting. All publications, patent applications, patents, and other references mentioned herein are incorporated by reference in their entirety. In case of conflict, the present

specification, including definitions, will control. All the sequences disclosed in the sequence listing are meant to be double-stranded except the sequences of oligonucleotides.

Other features and advantages of the invention will be apparent from the following detailed description, and from the claims.

Brief Description of the Drawings

Fig. 1A is a physical map of the MM locus. Arrows indicate the five new polymorphic markers and filled, vertical rectangular boxes indicate the previously known polymorphic markers. The five ESTs that are expressed in skeletal muscle are highlighted in bold. Detailed information on the minimal tiling path of the PAC contig spanning the MM/LGMD2B region is provided in Liu et al., 1998, *Genomics* 49:23-29. The minimal candidate MM region is designated by the solid bracket (top) and compared to the previous candidate region (dashed bracket). TGFA and ADD2 are transforming growth factor alpha and β-adducin 2.

Fig. 1B is a representation of the dysferlin cDNA clones. The probes used in the three successive screens are shown in bold (130347, cDNA10, A27-F2R2). The two most 5′ cDNA clones are also shown (B22, B33). The 6.9 kb cDNA for dysferlin (SEQ ID NO:1) is illustrated at the bottom with start and stop codons as shown.

Fig. 1C is a representation of the predicted dysferlin protein. The locations of four C2 domains (SEQ ID NOs: 86-89) are indicated by stippled boxes, while the putative transmembrane region is hatched. Vertical lines above the cDNA denote the positions of the mutations in Table 2; the associated labels indicate the phenotypes (MM - Miyoshi myopathy; LGMD - limb girdle

muscular dystrophy; DMAT - distal myopathy with anterior tibial onset).

Fig. 2 is the sequence of the predicted 2,080 amino acids of dysferlin (SEQ ID NO:2). The predicted membrane spanning residues are in bold at the carboxy terminus (residues 2047-2063). Partial C2 domains are underlined. Bold, underlined sequences are putative nuclear targeting residues. Possible membrane retention sequences are enclosed within a box.

Fig. 3 is a comparison of the Kyle-Doolittle hydrophobicity plots of the dysferlin protein and fer-1. On the Y-axis, increasing positivity corresponds to increasing hydrophobicity. Both proteins have a single, highly hydrophobic stretch at the carboxy terminal end (arrow). Both share regions of relative hydrophilicity approximately at residue 1,000 (arrowhead).

Fig. 4 is a SSCP analysis of a representative pedigree with dysferlin mutations. Each member of the pedigree is illustrated above the corresponding SSCP analysis. For each affected individual (solid symbols) shifts are evident in alleles 1 and 2, corresponding respectively to exons 36 and 54. As indicated, the allele 1 and 2 variants are transmitted respectively from the mother and the father. The two affected daughters in this pedigree have the limb girdle muscular dystrophy (LGMD) phenotype while their affected brother has a pattern of weakness suggestive of Miyoshi myopathy (MM).

Fig. 5 is a representation of the genomic structure of dysferlin. The 55 exons of the dysferlin gene and their corresponding SEQ ID NOs are indicated below the 6911 bp cDNA (solid line). The cDNA sequences corresponding to SEQ ID NO:1 and SEQ ID NO:3 are shown relative to the 6911 bp cDNA.

Figs. 6A-B are the cDNA sequence of brain-specific dysferlin (SEQ ID NO:232) and the predicted amino acid

sequence (in single-letter code) of brain-specific dysferlin (SEQ ID NO:233).

Detailed Description

The Miyoshi myopathy (MM) locus maps to human chromosome 2p12-14 between the genetic markers D2S292 and D2S286 (Bejaoui et al., 1995, *Neurology* 45:768-72). Further refined genetic mapping in MM families placed the MM locus between markers GGAA-P7430 and D2S2109 (Bejaoui et al., 1998, *Neurogenetics* 1:189-96). Independent investigation has localized the limb-girdle muscular dystrophy (LGMD-2B) to the same genetic interval (Bashir et al., 1994, *Hum. Molec. Genetics* 3:455-57; Bashir et al., 1996, *Genomics* 33:46-52; Passos-Bueno et al., 1995, *Genomics* 27:192-95). Furthermore, two large, inbred kindreds have been described whose members include both MM and LGMD2B patients (Weiler et al., 1996, *Am. J. Hum. Genet.* 59:872-78; Illarioshkin et al., 1997, *Genomics* 42:345-48). In these familial studies, the disease gene(s) for both MM and LGMD2B mapped to essentially the same genetic interval. Moreover, in both pedigrees, individuals with MM or LGMD2B phenotypes share the same haplotypes. This raises the intriguing possibility that the two diseases may arise from the same gene defect and that a particular disease phenotype is the result of modification by additional factors.

A 3-Mb PAC contig spanning the entire MM/LGMD2B candidate region was recently constructed to facilitate the cloning of the MM/LGMD2B gene(s) (Liu et al., 1998, *Genomics* 49:23-29). This high resolution PAC contig resolved the discrepancies of the order of markers in previous studies (Bejaoui et al., 1998, *Neurogenetics* 1:189-96; Bashir et al., 1996, *Genomics* 33:46-52; Hudson et al., 1995, *Science* 270:1945-54). The physical size of the PAC contig also indicated that the previous minimal

size estimation based on YAC mapping data was significantly underestimated.

Identification of Repeat Sequences and Repeat Typing

The PAC contig spanning the MM/LGMD2B region (Liu et al., 1998, *Genomics* 49:23-29) was used as a source for the isolation of new informative markers to narrow the genetic interval of the disease gene(s). DNA from the PAC clones spanning the MM/LGMD2B region was spotted onto Hybond N+™ membrane filters (Amersham, Arlington Heights, IL). The filters were hybridized independently with the following γ-^{32}P (Du Pont, Wilmington, DE) labeled repeat sequences: (1) $(CA)_{15}$; (2) pool of $(ATT)_{10}$, $(GATA)_8$ and $(GGAA)_8$; (3) pool of $(GAAT)_8$, $(GGAT)_8$ and $(GTAT)_8$; and (4) pool of $(AAG)_{10}$ and $(ATC)_{10}$. Hybridization and washing of the filters were carried out at 55°C following standard protocols (Sambrook et al., 1989, *Molecular Cloning: A Laboratory Manual* (2nd Edition), Cold Spring Harbor Press, N.Y.).

Miniprep DNAs of PAC clones containing repeat sequences were digested with restriction enzymes *Hind*III and *Pst*I and ligated into pBluescript II (KS+) vector which is (Stratagene, La Jolla, CA) digested with the same enzymes. Filters of the PAC subclones were hybridized to the γ-^{32}P labeled repeats that detected the respective PACs. For clones with an insert size greater than 1 kb the repeat sequences of which could not be identified by a single round of sequencing, the inserts were further subcloned by digestion with *Hae*III and ligation in *Eco*RV-digested pZero-2.1 vector (Invitrogen, Inc., Carlsbad, CA). Miniprep DNAs of the positive subclones were subjected to manual dideoxy sequencing with Sequenase™ enzyme (US Biochemicals, Inc., Cleveland, OH). Primer pairs for amplifying the repeat sequences were selected using the computer program Oligo (Version

4.0, National Biosciences, Inc., Plymouth, MN). Primer sequences are shown in Table 1.

TABLE 1

New Polymorphic Markers Mapped to the MM/LGMD2B Region

Marker	Repeat	Primers (5' to 3')	Annealing Tm (°C)	Size in PAC (bp)	No. of alleles[1]	Het[2]
PAC3-H52	CA	GATCTAACCCTGCTGCTCACC (SEQ ID NO:120) CTGGTGTGTTGCAGAGCGCTG (SEQ ID NO:121)	57	138	10	0.82
Cy172-H32[3]	CCAT	CCTCTCTTCTGCTGTCTTCAG (SEQ ID NO:122) TGTGTCTGGTTCCACCTTCGT (SEQ ID NO:123)	56	199	7	0.72
PAC35-PH2	CAT	TCCAAATAGAAATGCCTGAAC (SEQ ID NO:124) AGGTATCACCTCCAAGTGTTG (SEQ ID NO:125)	56	161	5	0.30
PAC16-H41	Complex	TACCAGCTTCAGAGCTCCCTG (SEQ ID NO:126) TTGATCAGGGTGCTCTTGG (SEQ ID NO:127)	58	280	4	0.41
Cy7-PH3	AAGG	GGAGAATTGCTTGAACCCAG (SEQ ID NO:128) TGGCTAATGATGTTGAACATTT (SEQ ID NO:129)	56	211	4	0.32

[1] Observed in 50 unrelated caucasians.
[2] Heterozygosity index.
[3] Located within intron 2 of the *dysferlin* gene.

All oligonucleotides were synthesized by Integrated DNA Technologies, Inc. (Coralville, IA). PCR typing of the repeat markers followed previously described protocols (Bejaoui et al., 1995, *Neurology* 45:768-772).

Identification of Repeat Markers and Haplotype Analysis

After hybridization with labeled repeat oligos, 17 different groups of overlapping PACs were identified that contained repeat sequences. Some groups contained previously identified repeat markers. For example, five groups of PACs were positively identified by a pool of repeat probes including $(ATT)_{10}$, $(GATA)_8$, and $(GGAA)_8$. Of these, three groups contained known markers GGAA-P7430 (GGAA repeat), D2S1394 (GATA repeat) and D2S1398 (GGAA repeat) (Hudson et al., 1992, *Nature* 13:622-29; Gastier et al., 1995, *Hum. Molecular Genetics* 4:1829-36). No attempt was made to isolate new repeat markers from these PACs and they were not further analyzed. Similarly, seven groups of PACs that contained known CA repeat markerswere excluded. Seven groups of PACs that contained unidentified repeats were retained for further analysis. For each group, the PAC containing the smallest insert was selected for subcloning. Subclones were re-screened and positive clones were sequenced to identify repeats. In total, seven new repeat sequences were identified within the MM/LGMD2B PAC contig. Of these, five are polymorphic within the population that was tested. The information for these five markers is summarized in Table 1. Based on the PAC contig constructed previously across the MM candidate locus (Liu et al., 1998, *Genomics* 48:23-29), the five new markers and ten previously published polymorphic markers were placed in an unambiguous order (Fig. 1).

These markers were analyzed in a large, consanguineous MM family (Bejaoui et al., 1995, *Neurology* 45: 768-72; Bejaoui et al., 1998, *Neurogenetics* 1:189-96). Because MM is a recessive condition, the locus can be defined by identifying regions of the genome that show homozygosity in affected individuals. Conversely, because of the high penetrance of this adult-onset

condition, unaffected adult individuals are not expected to be homozygous by descent across the region. Analysis of haplotype homozygosity in this pedigree indicates that the disease gene lies between markers D2S2111 and PAC3-H52. Based on the PAC mapping data, the physical distance for this interval is approximately 2.0 Mb. No recombination events were detected between four informative markers (markers cy172-H32 to PAC16-H41) and the disease locus in family MM-21 (Fig. 1A).

Identification of Five Muscle-Expressed ESTs

Twenty-two ESTs and two genes (transforming growth factor alpha [TGFα] and beta-adducin [ADD2]) were previously mapped to the MM/LGMD2B PAC contig (Fig. 1A) (Liu et al., 1998, *Genomics* 48:23-29). Two μl (approximately 0.1 ng/μl) of Marathon-ready™ skeletal muscle cDNA (Clontech, Palo Alto, CA) were used as template in a 10 μl PCR reaction for analysis of muscle expression of ESTs. The PCR conditions were the same as for the PCR typing of repeat markers. PCR analysis of skeletal muscle cDNA indicated that five of these ESTs (A006G04, stSG1553R, WI-14958, TIGR-A004Z44 and WI-14051) map within the minimal genetic MM interval of MM and are expressed in skeletal muscle.

Probes were selected corresponding to each of these five ESTs for Northern blot analysis. cDNA clones (130347, 48106, 172575, 184080, and 510138) corresponding to the five ESTs that are expressed in muscle (respectively TIGR-A004Z44, WI-14051, WI-14958, stSG1553R and A006G04) were selected from the UniGene database (http:/www.ncbi.nlm.nih.gov/UniGene/) and obtained from Genome Systems, Inc. (St. Louis, MO). The cDNA probes were first used to screen the MM/LGMD2B PAC filters to confirm that they mapped to the expected position in the MM/LGMD2B contig.

A Northern blot (Clontech) of multiple human tissues was sequentially hybridized to the five cDNA probes and a control β-actin cDNA at 65°C following standard hybridization and washing protocols (Sambrook et al., *supra*). Between hybridizations, probes were removed by boiling the blot at 95-100°C for 4-10 min with 0.5% SDS. The blot was then re-exposed for 24 h to confirm the absence of previous hybridization signals before proceeding with the next round of hybridization.

The tissue distribution, intensity of the signals and size of transcripts detected by the five cDNA probes varied. Probes corresponding to ESTs stSG1553R, TIGR-A004Z44 and WI-14958 detected strong signals in skeletal muscle. In addition, the cDNA corresponding to TIGR-A004Z44 detected a 3.6-3.8 kb brain-specific transcript instead of the 8.5 kb message that was present in other tissues. It is likely that these five ESTs correspond to different genes since the corresponding cDNA probes used for Northern analysis derive from the 3' end of messages, map to different positions in the MM/LGMD2B contig (Fig. 1A), and differ in their expression patterns.

Current database analysis suggests that three of these ESTs (stSG1553R, WI-14958 and WI-14051) do not match any known proteins (Schuler et al., 1996, Science 274:540-46). A006G04 has weak homology with a protein sequence of unknown function that derives from *C. elegans*. TIGR-A004Z44 has homology only to subdomains present within protein kinase C. Because the five genes corresponding to the ESTs are expressed in skeletal muscle and map within the minimal genetic interval of the MM/LGMD2B gene(s), they are candidate MM/LGMD2B gene(s).

Cloning of Dysferlin cDNA

EST TIGR-A004Z44 gave a particularly strong skeletal muscle signal on the Northern blot. Moreover, it is bracketed by genetic markers that show no recombination with the disease phenotype in family MM-21 (Fig. 1). The corresponding transcript was therefore cloned and analyzed as a candidate MM gene. From the Unigene database, a cDNA IMAGE clone (130347, 979 bp) was identified that contained the 483 bp EST TIGR-A004Z44.

Approximately 1 x 10^6 recombinant clones of a λgt11 human skeletal muscle cDNA library (Clontech) were plated and screened following standard techniques (Sambrook et al., *supra*). The initial library screening was performed using the insert released from the clone 130347 that contains EST TIGR-A0044Z44, corresponding to the 3' end of the gene. Positive phages were plaque purified and phage DNA was isolated according to standard procedures (Sambrook et al., *supra*). The inserts of the positive clones were released by *EcoR*I digestion of phage DNA and subsequently subcloned into the *EcoR*I site of pBluescript II (KS+) vector (Stratagene).

Fifty cDNA clones were identified when a human skeletal muscle cDNA library was screened with the 130347 cDNA. Clone cDNA10 with the largest insert (~6.5 kb) (Fig. 1B) was digested independently with *BamH*I and *Pst*I and further subcloned into pBluescript vector. Miniprep DNA of cDNA clones and subclones of cDNA10 was prepared using the Qiagen plasmid Miniprep kit (Valencia, CA). Sequencing was carried out from both ends of each clone using the SequiTherm EXCEL™ long-read DNA sequencing kit (Epicenter, Madison, WI), fluorescent-labeled M13 forward and reverse primers, and a LI-COR sequencer (Lincoln, NE). Assembly of cDNA contigs and sequence analysis were performed using Sequencher software (Gene Codes Corporation, Inc., Ann Arbor, MI).

Two additional screens, first with the insert of cDNA10 and then a 683 bp PCR product (A27-F2R2) amplified from the 5' end of the cDNA contig, identified 87 additional cDNA clones. Clones B22 and B33 extended the 5' end by 94 and 20 bp, respectively. The compiled sequence allowed for the generation of a sequence of 6.9 kb (SEQ ID NO:1) (with 10-fold average coverage).

Although the 5' end of the gene has not been further extended to the 8.5 kb predicted by Northern analysis, an open reading frame (ORF) of 6,243 bp has been identified within this 6.9 kb sequence. This ORF is preceded by an in-frame stop codon and begins with the sequence cgcaagc*ATG*CTG (SEQ ID NO:118); five of the first seven bp are consistent with the Kozak consensus sequence for a start codon (Kozak, 1989, *Nucl. Acids Res.* 15:8125-33; Kozak, 1989, *J. Cell. Biol.* 108:229-41). An alternate start codon, in the same frame, +75 bp downstream, appears less likely as a start site GAGACG*ATG*GGG (SEQ ID NO:119). Thus, the entire coding region of this candidate gene is believed to have been identified, as represented by the 6.9 kb sequence contig.

Isolation of the Brain-Specific Dysferlin Isoform

Identification of the brain-specific isoform of dysferlin

A brain-specific isoform of dysferlin was identified using Northern blot analysis of poly(A+)RNA derived from multiple human adult tissues probed with radiolabeled full-length dysferlin cDNA subclones. A prominent 7.2 kb transcript was detected on Northern blots in skeletal muscle, heart, placenta, lung, and kidney, while a distinct but equally prominent 3.6 kb-3.8 kb transcript was identified exclusively in the brain. Using long exposures, a faint 7.2 kb mRNA was also detected in the

brain. This finding suggested that the shorter brain isoform was likely to be a tissue-specific splice variant of the dysferlin gene. To test this hypothesis, a human brain cDNA library (Stratagene) was screened for the dysferlin brain isoform.

Cloning of the brain-specific dysferlin isoform

To identify probes that hybridize to the brain-specific dysferlin sequence and so could be used for library screening, fragments of the full-length dysferlin cDNA clone (derived from a skeletal muscle cDNA library) were generated using restriction enzymes. The fragments were about 1 kb in length and were analyzed by hybridization to a Northern blot that included brain RNA. Sequences suitable for library screening were those that hybridized to the 3.6-3.8 kb brain-specific transcript. A region of the 3' end of the dysferlin cDNA sequence that is approximately 3 kb in length was identified as hybridizing to brain mRNA. DNA containing sequence from this region was used as a probe for hybridization screening of a human brain cDNA library (Stratagene).

The human brain cDNA library was plated out and screened using standard procedures. Of the approximately 720,000 plaques screened, 63 primary positive clones were identified. Of these, 20 clones were selected for further analysis involving standard methods of hybridization, restriction enzyme mapping, and sequencing. The primary positive clones shared regions of overlap with each other.

Sequencing of positive clones, provided 3671 nucleotides of the brain-specific dysferlin sequence (SEQ ID NO:232; Figure 6A-B). The identified sequence corresponds closely to the size of the brain-specific dysferlin transcript detected on Northern blots. With the exception of the 5' region of the sequence, the

brain-specific sequence is identical to about 3.1 kb of the dysferlin sequence (from nucleotide 3722 to 6904 of the dysferlin sequence). In the dysferlin gene, position 3722 corresponds to the start of exon 32. This finding is consistent with the hypothesis that the brain isoform is a splice-variant of the dysferlin gene. At the 5' end of the brain isoform, 489 nucleotides are unique to brain-specific dysferlin. The amino acid sequence encoded by the brain dysferlin nucleic acid sequence (SEQ ID NO:233; Figure 6) contains a unique sequence with an initiation codon within a Kozak consensus sequence. The nucleic acid sequence unique to brain-specific dysferlin encodes a novel 24 amino acid sequence.

Identification of Mutations in Miyoshi Myopathy

Two strategies were used to determine whether this 6.9 kb cDNA (SEQ ID NO:1) is mutated in MM. First, the genomic organization of the corresponding gene was determined and the adjoining intronic sequence at each of the 55 exons which make up the cDNA was identified. To identify exon-intron boundaries within the gene, PAC DNA was extracted with the standard Qiagen -Mini Prep protocol. Direct sequencing was performed with DNA Sequence System (Promega, Madison, WI) using ^{32}P end-labeled primers (Benes et al., 1997, *Biotechniques* 23:98-100). Exon-intron boundaries were identified as the sites where genomic and cDNA sequences diverged. Second, in patients for whom muscle biopsies were available, RT-PCR was also used to prepare cDNA for the candidate gene from the muscle biopsy specimen.

Single strand conformational polymorphism analysis (SSCP) was used to screen each exon in patients from 12 MM families. Putative mutations identified in this way were confirmed by direct sequencing from genomic DNA using exon-specific intronic primers. Approximately 20

ng of total genomic DNA from immortalized lymphocyte cell lines were used as a template for PCR amplification analysis of each exon using primers (below) located in the adjacent introns. SSCP analysis was performed as previously described (Aoki et al., 1998, *Ann. Neurol.* 43:645-53). In patients for whom muscle biopsies were available, mRNA was isolated using RNA-STAT-60™ (Tel-Test, Friendswood, TX) and first-strand cDNA was synthesized from 1-2 μg total RNA with MMLV reverse transcriptase and random hexamer primers (Life Technologies, Gaithersburg, MD). Three μl of this product were used for PCR amplification. Eight sets of primers were designed for muscle cDNA, and overlapping cDNA fragments suitable for SSCP analysis were amplified. After initial denaturation at 94°C for 2 min, amplification was performed using 30 cycles at 94°C for 30 s, 56°C for 30 s, and 72°C for 60 s. The sequences of polymorphisms detected by SSCP analysis were determined by the dideoxy termination method using the Sequenase kit (US Biochemicals). In some instances, the base pair changes predicted corresponding changes in restriction enzyme recognition sites. Such alterations in restriction sites were verified by digesting the relevant PCR products with the appropriate restriction enzymes.

Primer pairs used for SSCP screening and exon sequencing are as follows:

(1) exon 3, F3261 5'-tctcttctcctagagggccatag-3' (SEQ ID NO: 101) and R326 5'-ctgttcctccccatcgtctcatgg-3' (SEQ ID NO: 102);

(2) exon 20, F3121 5'-gctcctcccgtgaccctctg-3' (SEQ ID NO: 103) and R3121 5'-gggtcccagccaggagcactg-3' (SEQ ID NO: 104);

(3) exon 36, F2102 5'-cccctctcaccatctcctgatgtg-3' (SEQ ID NO: 105) and R2111 5'-tggcttcaccttccctctacctcgg-3' (SEQ ID NO: 106);

(4) exon 49, F1081 5'-tcctttggtaggaaatctaggtgg-3' (SEQ ID NO: 107) and R1081 5'-ggaagctggacaggcaagagg-3' (SEQ ID NO: 108);

(5) exon 50, F1091 5'-atatactgtgttggaaatcttaatgag-3' (SEQ ID NO: 109) and R1091 5'-gctggcaccacagggaatcgg-3' (SEQ ID NO: 110);

(6) exon 51, F1101 5'-ctttgcttccttgcatccttctctg-3' (SEQ ID NO: 111) and R1101 5'-agcccccatgtgcagaatggg-3' (SEQ ID NO: 112);

(7) exon 52, F1111 5'-ggcagtgatcgagaaacccgg-3' (SEQ ID NO: 113) and R1111 5'-catgccctccactggggctgg-3' (SEQ ID NO: 114);

(8) exon 54, F1141 5'-ggatgcccagttgactccggg-3' (SEQ ID NO: 115) and R1141 5'-ccccaccacagtgtcgtcagg-3' (SEQ ID NO: 116);

(9) exon 29, F3031 5'-aagtgccaagcaatgagtgaccgg-3' (SEQ ID NO: 184) and R3021 5'-ctcactcccacccaccacctg-3' (SEQ ID NO: 185);

(10) exon 31, F2141 5'-gaatctgccataaccagcttcgtg-3' (SEQ ID NO: 188) and R2141 5'-tatcaccccatagaggcctcgaag-3' (SEQ ID NO: 189);

(11) exon 32, F2981 5'-cagccactcactctggcacctctg-3' (SEQ ID NO: 190) and R2981 5'-agcccacagtctctgactctcctg-3' (SEQ ID NO: 191);

(12) exon 43, F2031 5'-cagccaaaccatatcaacaatg-3' (SEQ ID NO: 210) and R2021 5'-ctggggaggtgagggctctag-3' (SEQ ID NO: 211);

(13) exon 44, F2011 5'-gaagtgttttgtctcctcctc-3' (SEQ ID NO: 212) and R2011 5'-gcaggcagccagcccccatc-3' (SEQ ID NO: 213);

(14) exon 46, F1041 5'-ctcgtctatgtcttgtgcttgctc-3' (SEQ ID NO: 216) and R1051 5'-caccatggtttggggtcatgtgg-3' (SEQ ID NO: 217).

These primers were used in SSCP screening and exon sequencing, and identified eighteen different mutations in fifteen families (Table 2).

Table 2

Mutations in Dysferlin in Distal Myopathy and LGMD[1]

Name	Nucleotide Change	Exon	Consequence	Origin	Family name	Allele	Change of restriction site
Mutations							
537insA	ins of A at 537	3	Frameshift	Arabic	MM59	Hom	no change
Q605X	CAG to TAG at 2186	20	Stop at 605	French	MM67	Hom	-Pst I, -Fnu 4H I[1]
I1298V	ATC to GTC at 4265	36	Amino acid change	Italian	MM, LGMD56	Het	-BamHI, -BStYI; +Ava II
E1883X	GAG to TAG at 5870	49	Stop at 1883	English	MM8	Het	no change
H1857R	CAT to CGT at 5943	50	Amino acid change	English	MM50	Het	no change

	5966delG	del of G at 5966	50	Frameshift	Spanish	DMAT71	Hom	no change
	5966delG	del of G at 5966	50	Frameshift	Spanish	MM75	Hom	no change
	6071/6072delAG	del of AG at 6071/6072	51	Frameshift	English	MM58	Het	no change
	6319+1G to A	Ggt to Gat at 6319+1	52	5′ splice site	English	MM8	Het	no change
	R2042C	CGT to TGT at 6497	54	Amino acid change	Italian	MM56	Het	-Fnu4HI
	R1046H	CGC to CAG at 3510	29	Amino acid change	Japanese	MM10	Hom	-HinPI, -Fsp I
	3746delG	del of G at 3746	31	Frameshift	Japanese	MM17	Hom	-MboII
	Q1160X	CAG to TAG at 3851	32	Stop at 1160	Mexican	MM46	Hom	-ScrFI, -BstNI, +MaeI, +BfaI

5122/5123delCA	del of CA at 5122/5123, A to T at 5121	43	Frameshift	Japanese	MM14	Het	no change
R1586X	CGA to TGA at 5129	43	Stop at 1586	Japanese	MM12	Hom	+Dde I
5245delG	del of G at 5245 and G to C at 5249, or G to C at 5245 and del G at 5249	44	Frameshift	French	MM63	Hom	-Bpm I, -BanII + AvaII, +Sau96I
E1732X	GAG to TAG at 5567	46	Stop at 1732	Spanish	MM73	Het	-Mbo II
2573-77 Hom del ACCCA	Del of ACCCA at 2573-77 ?Please provide	23	Frameshift	Italian	MM69		

[1] MM: Miyoshi myopathy; DMAT: distal myopathy with anterior tibial onset; LGMD: limb girdle muscular dystrophy

[2] +: create a new restriction site, -: eliminate an existing restriction site.

Twelve of the eighteen different mutations are predicted to block dysferlin expression, either through nonsense or frameshift changes. Seven of the thirteen samples are homozygous and thus expected to result in complete loss of dysferlin function. For each mutated exon in these patients, at least 50 control DNA samples (100 chromosomes) were screened to determine the frequencies of the sequence variants. When possible, the parents and siblings of affected individuals were also screened to verify that defined mutations were appropriately co-inherited with the disease in each pedigree (Fig. 4). In two families (50, 58 in Table 2) heterozygous mutations were identified in one allele (respectively a missense mutation and a 2 bp deletion). Mutations in the other allele are presumed to have not been detected (or in three of the screened MM families) either because the mutant and normal SSCP products are indistinguishable or because the mutation lies outside of coding sequence (i.e., in the promoter or a regulatory region of an intron). The disease-associated mutations did not appear to arise in the population as common polymorphisms.

More mutations can be identified by using appropriate primer pairs to amplify an exon and analyze its sequence. The following primer pairs are useful for exon amplification.

Exon	Code	Primer Sequence
1	F408	5'-gacccacaagcggcgcctcgg-3'{SEQ ID NO: 130}
	F4101	5'-gaccccggcgagggtggtcgg-3'{SEQ ID NO: 131}
2	F4111	5'-tgtctctccattctccctttgtg-3'{SEQ ID NO:132}
	R4111	5'-aggacactgctgagaaggcacctc-3'{SEQ ID NO: 133}

3 F3262 5-agtgccctggtggcacgaagg-3' {SEQ ID NO: 134}
R3261 5-cctacctgcaccttcaagccatgg-3' {SEQ ID NO: 135}
4 F3251 5-cagaagagccagggtgccttagg-3' {SEQ ID NO: 136}
R3251 5-ccttggaccttaacctggcagagg-3' {SEQ ID NO: 137}
5 F3242 5-cgaggccagcgcaccaacctg-3' {SEQ ID NO: 138}
R3242 5-actgccggccattcttgctggg-3' {SEQ ID NO: 139}
6 F3231 5-ccaggcctcattagggccctc-3' {SEQ ID NO: 140}
R3231 5-ctgaagaggagcctggggtcag-3' {SEQ ID NO: 141}
7 F3222 5-ctgagatttctgactcttggggtg-3' {SEQ ID NO: 142}
R3211 5-aaggttctgccctcatgccccatg-3' {SEQ ID NO: 143}
8 F3561 5-ctggcctgagggatcagcagg-3' {SEQ ID NO: 144}
R3561 5-gtgcatacatacagcccacggag-3' {SEQ ID NO: 145}
9 F3551 5-gagctattgggttggccgtgtggg-3' {SEQ ID NO: 146}
R3552 5-accaacacggagaagtgagaactg-3' {SEQ ID NO: 147}
10 F3201 5-ccacactttatttaacgctttggcgg-3'{SEQ ID NO: 148}
R3201 5-cagaaccaaaatgcaaggatacgg-3' {SEQ ID NO: 149}
11 F3191 5-cttctgattctgggatcaccaaagg-3' {SEQ ID NO: 150}

F3191 5-ggaccgtaaggaagacccaggg-3' {SEQ ID NO: 151}

12 F3181 5-cctgtgctcaggagcgcatgaagg-3'{SEQ ID NO: 152}

R3181 5-gcagacctcccacccaagggcg-3' {SEQ ID NO: 153}

13 F3171 5-gagacagatgggggacagtcaggg-3' {SEQ ID NO: 154}

R3171 5-cctcccgagagaaccctcctg-3' {SEQ ID NO: 155}

14 F3161 5-gggagcccagagtccccatgg-3' {SEQ ID NO: 156}

R3161 5-gggcctccttgggtttgctgg-3' {SEQ ID NO: 157}

15 F3541 5-gcctccccagcatcctgccgg-3' {SEQ ID NO: 158}

R3541 5-tcactgagccgaatgaaactgagg-3' {SEQ ID NO: 159}

16 F3531 5-tgtggcctgagttcctttcctgtg-3' {SEQ ID NO: 160}

R3531 5-ggtcaaagggcagaacgaagaggg-3' {SEQ ID NO: 161}

17 F3151 5-cccgtccttctcccagccatg-3' {SEQ ID NO: 162}

R3151 5-ctcccctggttgtccccaagg-3' {SEQ ID NO: 163}

18 F3141 5-cgacccctctgattgccacttgtg-3' {SEQ ID NO: 164}

R3141 5-ggcatcctgcccttgccaggg-3' {SEQ ID NO: 165}

19 F3522 5-tctgtctcccctgctccttg-3' {SEQ ID NO: 166}

R3522 5-cttccctgccccgacgcccag-3' {SEQ ID NO: 167}

20 F3121 5-gctcctcccgtgaccctctgg-3' {SEQ ID NO: 103}

R3121 5-gggtcccagccaggagcactg-3' {SEQ ID NO: 104}

21 F3111 5-cagcgctcaggcccgtctctc-3' {SEQ ID NO: 168}

R3111 5-tgcataggcatgtgcagctttggg-3' {SEQ ID NO: 169}

22 F3512 5-catgcaccctctgccctgtgg-3' {SEQ ID NO: 170}

R3512 5-agttgagccaggagaggtggg-3' {SEQ ID NO: 171}

23 F3101 5-catcaggcgcattccatctgtccg-3' {SEQ ID NO: 172}

R3091 5-agcaggagagcagaagaagaaagg-3' {SEQ ID NO: 173}

24 F3082 5-gtgtgtcaccatccccaccccg-3' {SEQ ID NO: 174}

R3082 5-caagagatgggagaaaggccttatg-3' {SEQ ID NO:175}

25 F3073 5-ctgggacatccggatcctgaagg-3' {SEQ ID NO: 176}

R3073 5-tccaggtagtgggaggcagagg-3' {SEQ ID NO: 177}

26 F3061 5-tcccactacctggagctgccttgg-3' {SEQ ID NO: 178}

R3051 5-ggctctccccagccctccctg-3' {SEQ ID NO: 179}

27 F3601 5-cagagcagcagagactctgaccag-3' {SEQ ID NO: 180}

R3601 5-tagaccccacctgcccctgag-3' {SEQ ID NO: 181}

28 F3501 5-tcctctcattgcttgcctgttcgg-3' {SEQ ID NO: 182}

R3501 5-ttgagagcttgccggggatgg-3' {SEQ ID NO: 183}

29 F3031 5-aagtgccaagcaatgagtgaccgg-3' {SEQ ID NO: 184}

R3021 5-ctcactcccacccaccacctg-3' {SEQ ID NO: 185}

30 F3011 5-cccaccggcctctgagtctgc-3' {SEQ ID NO: 186}

R3001 5-accctacccaagccaggacaagtg-3' {SEQ ID NO: 187}

31 F2141 5-gaatctgccataaccagcttcgtg-3' {SEQ ID NO: 188}

R2141 5-tatcaccccatagaggcctcgaag-3' {SEQ ID NO: 189}

32 F2981 5-cagccactcactctggcacctctg-3' {SEQ ID NO: 190}

R2981 5-agcccacagtctctgactctcctg-3' {SEQ ID NO: 191}

33 F2131 5-acatctctcagggtccctgctgtg-3' {SEQ ID NO: 192}

R2211 5-cctgtgaggggacgaggcagg-3' {SEQ ID NO: 193}

34 F2202 5-gccctgggtaagggatgctgattc-3' {SEQ ID NO: 194}

R2202 5-cctgcctgggcctcctggatc-3' {SEQ ID NO: 195}

35 F2111 5-gagggtgatgggggccttagg-3' {SEQ ID NO: 196}

R2112 5-gcaatcagtttgaagaaggaaagg-3' {SEQ ID NO: 197}

36 F2102 5-cccctctcaccatctcctgatgtg-3' {SEQ ID NO: 105}

R2111 5-ggcttcaccttccctctacctcgg-3' {SEQ ID NO: 106}

37 F2101 5-caccttgtctccattctacctgc-3' {SEQ ID NO: 198}
R2101 5-ctcccagcccccacgcccagg-3' {SEQ ID NO: 199}
38 F2091 5-ctgagccactctcctcattctgtg-3' {SEQ ID NO: 200}
R2091 5-tggaaggggacagtagggagg-3' {SEQ ID NO: 201}
39 F2081 5-ggccagtgcgttcttcctcctc-3' {SEQ ID NO: 202}
R2071 5-tccctgacctgcccatcatctc-3' {SEQ ID NO: 203}
40 F2061 5-gcccctgtcaggcctggatgg-3' {SEQ ID NO: 204}
R2061 5-tgacccaggcctccctggagg-3' {SEQ ID NO: 205}
41 F2051 5-ctgaaatggtctctttctttctac-3' {SEQ ID NO: 206}
R2051 5-cacaccgactgtcagactgaagag-3' {SEQ ID NO: 207}
42 F2041 5-ttgtcccctcctctaatccccatg-3' {SEQ ID NO: 208}
R2041 5-gggttagggacgtcttcgagg-3' {SEQ ID NO: 209}
43 F2031 5-cagccaaaccatatcaacaatg-3' {SEQ ID NO: 210}
R2021 5-ctggggaggtgagggctctag-3' {SEQ ID NO: 211}
44 F2011 5-gaagtgttttgtctcctcctc-3' {SEQ ID NO: 212}
R2011 5-gcaggcagccagcccccatc-3' {SEQ ID NO: 213}
45 F1021 5-gggtgccctgtgttggctgac-3' {SEQ ID NO: 214}

R1031 5-gcaggcagccagcccccatc-3' {SEQ ID NO: 215}

46 F1041 5-ctcgtctatgtcttgtgcttgctc-3' {SEQ ID NO: 216}

R1051 5-caccatggtttggggtcatgtgg-3' {SEQ ID NO: 217}

47 F1061 5-tctcgcttccccagctcctgc-3' {SEQ ID NO: 218}

R1061 5-tctggagttcgaggactctggg-3' {SEQ ID NO: 219}

48 F1071 5-agaagggtggggagagaacgg-3' {SEQ ID NO: 220}

R1071 5-cagctcagagcctgtggctgg-3' {SEQ ID NO: 221}

49 F1082 5-aaggccttcccatcctttggtagg-3' {SEQ ID NO: 222}

R1082 5-acaacccagagggagcacggg-3' {SEQ ID NO: 223}

50 F1092 5-gttgacgatgtatatactgtgttgg-3' {SEQ ID N0: 224}

R1091 5-gctggcaccacagggaatcgg-3' {SEQ ID NO: 110}

51 F1102 5-gcctctctctaactttgcttccttg-3' {SEQ ID NO: 225}

R1101 5-agcccccatgtgcagaatggg-3' {SEQ ID NO: 112}

52 F1112 5-ggctacaggctggcagtgatcgag-3' {SEQ ID NO: 226}

R1112 5-ttcccccatgccctccactgg-3' {SEQ ID NO: 227}

53 F1121 5-agccttcgtgcccctaaccaagtg-3' {SEQ ID NO: 228}

R1121 5-ctgtgggcattggggctcagg-3' {SEQ ID NO: 229}

54	F1141	5-ggatgcccagttgactccggg-3'	{SEQ ID NO: 115}
	R1141	5-ccccaccacagtgtcgtcagg-3'	{SEQ ID NO: 116}
55	F1151	5-gccccagtgggatcaccatg-3'	{SEQ ID NO: 230}
	R116	5-atgctggaggggaccccacgg-3'	{SEQ ID NO: 231}

Comparison of Dysferlin With Other Proteins

The 6,243 bp ORF of this candidate MM gene is predicted to encode 2,080 amino acids (Figs. 1C and 2; SEQ ID NO:2). At the amino acid level, this protein is highly homologous to the nematode (*Caenorhabditis elegans*) protein fer-1 (27% identical, 57% identical or similar: the sequence alignment and comparison was performed using http://vega.igh.cnrs.fr/bin/nph-align_query.pl.) (Argon & Ward, 1980, *Genetics* 96:413-33; Achanzar & Ward, 1997, *J. Cell Science* 110:1073-81). This *dys*trophy-associated, *fer*-1-*like* protein has therefore been designated "dysferlin."

The fer-1 protein was originally identified through molecular genetic analysis of a class of fertilization-defective *C. elegans* mutants in which spermatogenesis is abnormal (Argon & Ward, 1980, *Genetics* 96:413-33). The mutant fer-1 spermatozoa have defective mobility and show imperfect fusion of membranous organelles (Ward et al., 1981, *J. Cell Bio.* 91:26-44). Like fer-1, dysferlin is a large protein with an extensive, highly charged hydrophilic region and a single predicted membrane spanning region at the carboxy terminus (Fig. 3). There is a membrane retention sequence 3' to the membrane spanning stretch, indicating that the protein may be preferentially targeted to either endoplasmic or sarcoplasmic reticulum, probably as a Type II protein

(i.e. with the NH_2 end and most of the following protein located within the cytoplasm) (Fig. 1C). Several nuclear membrane targeting sequences are predicted within the cytoplasmic domain of the protein (http://psort.nibb.ac.jp/form.html). Immunocytochemical detection of dysferlin suggests that dysferlin is targeted to or anchored within the sarcoplasmic reticulum.

The cytoplasmic component of this protein contains four motifs homologous to C2 domains. C2 domains are intracellular protein modules composed of 80 - 130 amino acids (Rizo & Sudhof, 1998, *J. Biol. Chem.* 273:15897). Originally identified within a calcium-dependent isoform of protein kinase C (Nishizuka, 1988, *Nature* 334:661-65), C2 domains are present in numerous proteins. These domains often arise in approximately homologous pairs described as double C2 or DOC2 domains. One DOC2 protein, DOC2α, is brain specific and highly concentrated in synaptic vesicles (Orita et al., 1995, *Biochem. Biophys. Res. Comm.* 206:439-48), while another, DOC2β, is ubiquitously expressed (Sakaguchi et al., 1995, *Biochem. Biophys. Res. Comm.* 217:1053-61). Many C2 modules can fold to bind calcium, thereby initiating signaling events such as phospholipid binding. At distal nerve terminals, for example, the synaptic vesicle protein synaptotagmin has two C2 domains that, upon binding calcium, permit this protein to interact with syntaxin, triggering vesicle fusion with the distal membrane and neurotransmitter release (Sudhof & Rizo, 1996, *Neuron* 17:379-88).

The four dysferlin C2 domains are located at amino acid positions 32-82, 431-475, 1160-1241, and 1582-1660 (Figs. 1C and 3). Indeed, it is almost exclusively through these regions that dysferlin has homology to any proteins other than fer-1. Each of these segments in

dysferlin is considerably smaller than a typical C2 domain. Moreover, these segments are more widely separated in comparison with the paired C2 regions in synaptotagmin, DOC2α and β and related C2-positive proteins. For this reason, it is difficult to predict whether the four relatively short C2 domains in dysferlin function analogously to conventional C2 modules. That dysferlin might, by analogy with synaptotagmin, signal events such as membrane fusion is suggested by the fact that fer-1 deficient worms show defective membrane organelle fusion within spermatozoa (Ward et al., 1981, *J. Cell Bio.* 91:26-44).

The invention will be further described in the following examples, which do not limit the scope of the invention described in the claims.

EXAMPLES

Example 1: Production of dysferlin protein

Standard methods can be used to synthesize either wild type or mutant dysferlin, or fragments of either. These methods can also be used to synthesize brain-specific dysferlin polypeptides including full-length or fragments (e.g., a polypeptide unique to brain-specific dysferlin). For example, a recombinant expression vector encoding dysferlin (or a fragment thereof: e.g., dysferlin minus its membrane-spanning region) operably linked to appropriate expression control sequences can be used to express dysferlin in a prokaryotic (e.g., E.coli) or eukaryotic host (e.g., insect cells, yeast cells, or mammalian cells). The protein is then purified by standard techniques. If desired, DNA encoding part or all of the dysferlin sequence can be joined in-frame to DNA encoding a different polypeptide, to produce a chimeric DNA that encodes a hybrid polypeptide. This can be used, for example, to add a tag that will simplify identification or purification of the expressed protein,

or to render the dysferlin (or fragment thereof) more immunogenic.

The preferred means for making short peptide fragments of dysferlin is by chemical synthesis. These fragments, like dysferlin itself, can be used to generate antibodies, or as positive controls for antibody-based assays.

Fusion proteins are useful, e.g., for generating antibodies. Such fusion proteins are generated using known methods. In one example, to construct glutathione S-transferase (GST):dysferlin fusion proteins, the BLAST program (Altschul et al., 1990, J. Molec. Biol. 215:403-410) was used to identify three regions of the dysferlin cDNA that show no homology to any known human proteins (Figure 1). These were subcloned from the dysferlin cDNA as BstYI (881-1333), XmnI (1990-2718) and SalI (5364-5732) fragments ligated respectively into BamHI, SmaI and SalI sites of pGEX-5X-3 (Pharmacia). The three fragments correspond to amino acid sequences at amino acid locations 253-403, 624-865, and 1664-1786 of SEQ ID NO:2, respectively. The resulting GST fusion proteins of BamHI (43 kDa) and SmaI (53.3 kDa) formed isoluble aggregates that were isolated by SDS-PAGE. The fusion protein of SalI (40.2 kDa) was soluble and thus could be purified using a glutathione Sepharose 4B column; the SalI dysferlin fragment (14.2 kDa) was isolated by cleavage from GST using Factor Xa protease. The eluted protein was concentrated and further purified by SDS-PAGE. For all three of the fusion peptides, the resulting SDS-PAGE bands were excised and used to immunize rabbits.

Example 2: Production and characterization of anti-dysferlin antibodies

Techniques for generating both monoclonal and polyclonal antibodies specific for a particular protein

are well known. The antibodies can be raised against a short peptide epitope of dysferlin, an epitope linked to a known immunogen to enhance immunogenicity, a long fragment of dysferlin, or the intact protein. Antibodies can also be raised against brain-specific dysferlin polypeptides, e.g., against amino acids 1-24 of SEQ ID NO:233. Such antibodies raised against dysferlin or brain-specific dysferlin polypeptides are useful for e.g., localizing such polypeptides in tissue sections or fractionated cell preparations and diagnosing dysferlin-related disorders.

An isolated dysferlin protein, or a portion or fragment thereof, can be used as an immunogen to generate antibodies that bind dysferlin using standard techniques for polyclonal and monoclonal antibody preparation. The dysferlin immunogen can also be a mutant dysferlin or a fragment of a mutant dysferlin. A full-length dysferlin protein can be used or, alternatively, antigenic peptide fragments of dysferlin can be used as immunogens. The antigenic peptide of dysferlin comprises at least 8 (preferably 10, 15, 20, or 30) amino acid residues of the amino acid sequence shown in SEQ ID NO:2 and encompasses an epitope of such that an antibody raised against the peptide forms a specific immune complex with dysferlin. Preferred epitopes encompassed by the antigenic peptide are regions of dysferlin that are located on the surface of the protein, e.g., hydrophilic regions.

A dysferlin immunogen typically is used to prepare antibodies by immunizing a suitable subject (e.g., rabbit, goat, mouse or other mammal) with the immunogen. An appropriate immunogenic preparation can contain, for example, recombinantly expressed dysferlin protein or a chemically synthesized dysferlin polypeptide. The preparation can further include an adjuvant, such as Freund's complete or incomplete adjuvant, or similar

immunostimulatory agent. Immunization of a suitable subject with an immunogenic dysferlin preparation induces a polyclonal anti-dysferlin antibody response.

Polyclonal anti-dysferlin antibodies ("dysferlin antibodies") can be prepared as described above by immunizing a suitable subject with a dysferlin immunogen. The dysferlin antibody titer in the immunized subject can be monitored over time by standard techniques, such as with an enzyme linked immunosorbent assay (ELISA) using immobilized dysferlin. If desired, the antibody molecules directed against dysferlin can be isolated from the mammal (e.g., from the blood) and further purified by well-known techniques, such as protein A chromatography to obtain the IgG fraction. At an appropriate time after immunization, e.g., when the dysferlin antibody titers are highest, antibody-producing cells can be obtained from the subject and used to prepare monoclonal antibodies by standard techniques, such as the hybridoma technique originally described by Kohler and Milstein (1975) *Nature* 256:495-497, the human B cell hybridoma technique (Kozbor et al. (1983) *Immunol. Today* 4:72), the EBV-hybridoma technique (Cole et al. (1985), *Monoclonal Antibodies and Cancer Therapy*, Alan R. Liss, Inc., pp. 77-96) or trioma techniques. The technology for producing hybridomas is well known (*see generally Current Protocols in Immunology* (1994) Coligan et al. (eds.) John Wiley & Sons, Inc., New York, NY). Briefly, an immortal cell line (typically a myeloma) is fused to lymphocytes (typically splenocytes) from a mammal immunized with a dysferlin immunogen as described above, and the culture supernatants of the resulting hybridoma cells are screened to identify a hybridoma producing a monoclonal antibody that binds dysferlin.

Any of the many well known protocols used for fusing lymphocytes and immortalized cell lines can be applied

for the purpose of generating a monoclonal antibody against dysferlin (*see, e.g., Current Protocols in Immunology, supra*; Galfre et al. (1977) *Nature* 266:55052; R.H. Kenneth, in *Monoclonal Antibodies: A New Dimension In Biological Analyses*, Plenum Publishing Corp., New York, New York (1980); and Lerner (1981) *Yale J. Biol. Med.*, 54:387-402. Moreover, the one in the art will appreciate that there are many variations of such methods which also would be useful. Hybridoma cells producing a monoclonal antibody of the invention are detected by screening the hybridoma culture supernatants for antibodies that bind dysferlin, e.g., using a standard ELISA assay.

Alternative to preparing monoclonal antibody-secreting hybridomas, a monoclonal dysferlin antibody can be identified and isolated by screening a recombinant combinatorial immunoglobulin library (e.g., an antibody phage display library) with dysferlin to thereby isolate immunoglobulin library members that bind dysferlin. Kits for generating and screening phage display libraries are commercially available (e.g., the Pharmacia *Recombinant Phage Antibody System*, Catalog No. 27-9400-01; and the Stratagene *SurfZAP™ Phage Display Kit*, Catalog No. 240612). Additionally, examples of methods and reagents particularly amenable for use in generating and screening antibody display library can be found in, for example, U.S. Patent No. 5,223,409; PCT Publication No. WO 92/18619; PCT Publication No. WO 91/17271; PCT Publication No. WO 92/20791; PCT Publication No. WO 92/15679; PCT Publication No. WO 93/01288; PCT Publication No. WO 92/01047; PCT Publication No. WO 92/09690; PCT Publication No. WO 90/02809; Fuchs et al. (1991) *Bio/Technology* 9:1370-1372; Hay et al. (1992) *Hum. Antibod. Hybridomas* 3:81-85; Huse et al. (1989) *Science*

246:1275-1281; Griffiths et al. (1993) *EMBO J.* 12:725-734.

As an example, two polyclonal antisera were raised for each of the fusion peptide antigens described above using New Zealand White rabbits. The rabbits were injected with 0.5 mg of antigen using keyhole limpet hemocyanin (KLH) as the adjuvent. Booster injections of 0.25 mg antigen were administered every three weeks over 12 weeks. Serum was prepared from the rabbits and was purified using affinity column chromatography (HiTrap; Pharmacia) or antigen-blotted polyvinylidene difluoride (PVDF) membrane.

Immunoblotting was used to verify that the affinity-purified antisera recognize the cognate fusion peptides by Western immunoblotting (WIB) and that this reactivity was immunoadsorbed by pre-incubation of the antisera with the peptides. Thus, antiserum raised against the polypeptide encoded by the SalI fragment (encoding amino acids 1664-1786) identified the fragment both as a cleaved, 14.2 kDa fragment and as a component of the 40.2 kDa GST-SalI fusion peptide. No reactivity was evident in the fraction containing only the GST fusion partner. Immunoadsorption entirely abolished this staining. Analogous results were detected with all six antisera (to the three different target fusion peptides).

Preparation of subcellular fractions

Frozen human muscle (0.3 g) was homogenized in five volumes of 0.25 M sucrose containing proteinase inhibitor (Complete, Boehringer). Subcellular fractions of nuclei, mitochondria, microsomes, and cytosol were separated by differential centrifugation. The purity of each fraction was evaluated by immunoblotting of fraction-specific proteins with antibodies to histone H1 (Calbiochem), cytochrome c (Santa Cruz), Na^+-K^+ ATPase α1 subunit

(Research Diagnostics) and cytosolic superoxide dismutase (Calbiochem).

Dysferlin in subcellular fractions

Immunoblotting was used to analyze dysferlin expression. Twenty μg of each subcellular fraction and 40 μg of whole homogenate of muscle were separated by SDS-PAGE (4-15% gradient gel) and transferred to a nitrocellulose membrane. Immunoblotting was performed according to standard methods, using chemiluminescence (ECL, Amersham). Immunoblotting of multi-tissue blots identified prominent dysferlin positively at approximately 230 kDa in heart, placenta, skeletal muscle and kidney. Little or no immuno-positive staining was detected in brain, liver, spleen, ovary, or testis. Lower molecular weight bands (approximately 40 kDa) were also evident. Immunoadsorption with the corresponding fusion peptide abolished both the large and the smaller bands. The 230 kDa band was observed with all of the affinity purified, anti-dysferlin antisera.

Immunoblotting of fractionated human muscle documented distinct 230 kDa bands in the whole muscle homogenate an in microsomal and nuclear fractions. Some immunoreactivity was also evident in the nuclear and mitochondrial fractions. No immunoreactivity was detected in the cytosolic fractions. This pattern was seen with all of the anti-dysferlin antisera, and was eliminated by immunoadsorption. The identity of the assayed fractions was verified by Western blotting using fraction-specific antibodies: histone HI for the nuclear fraction, cytochrome c for the mitochondrial fraction, Na^+-K^+ ATPase α1-subunit for the microsomal fraction, and SOD1 for the cytosolic fraction.

Example 3: Diagnosis

The discovery of mutations in the dysferlin gene that are associated with the MM and LMGD2B phenotypes means that individuals can be tested for the disease gene before symptoms appear. This will permit genetic testing and counseling of those with a family history of the disease. Additionally, individuals diagnosed with the genetic defect can be closely monitored for the appearance of symptoms, thereby permitting early intervention, including genetic therapy, as appropriate. Individuals with a brain-specific dysferlin-related disorder can be diagnosed using such methods.

Diagnosis can be carried out on any suitable genomic DNA sample from the individual to be tested. Typically, a blood sample from an adult or child, or a sample of placental or umbilical cord cells of a newborn would be used; alternatively, one could utilize a fetal sample obtained by amniocentesis or chorionic villi sampling.

It is expected that standard genetic diagnostic methods can be used. For example, PCR can be utilized to identify the presence of a deletion, addition, or substitution of one or more nucleotides within any one of the exons of dysferlin. Following the PCR reaction, the PCR product can be analyzed by methods such as a heteroduplex detection technique based upon that of White et al. (1992, *Genomics* 12:301-06), or by techniques such as cleavage of RNA-DNA hybrids using RNase A (Myers et al., 1985, *Science* 230:1242-46), single-stranded conformation polymorphism (SSCP) analysis (Orita et al., 1989, *Genomics* 10:298-99), di-deoxy-fingerprinting (DDF) (Blaszyk et al., 1995, *Biotechniques* 18: 256-260) and denaturing gradient gel electrophoresis (DGGE; Myers et al., 1987, *Methods Enzymol.* 155:501-27). The PCR may be carried out using a primer which adds a G+C rich sequence (termed a "GC-clamp") to one end of the PCR product, thus improving the sensitivity of the subsequent DGGE

procedure (Sheffield et al., 1989, *Proc. Natl. Acad. Sci. USA* 86:232-36). If the particular mutation present in the patient's family is known to have removed or added a restriction site, or to have significantly increased or decreased the length of a particular restriction fragment, a protocol based upon restriction fragment length polymorphism (RFLP) analysis (perhaps combined with PCR) may be appropriate.

The apparent genetic heterogeneity resulting in the MM/LGMD2B phenotypes means that the nature of the particular mutation carried by affected individuals in the patient's family may have to be ascertained prior to attempting genetic diagnosis of the patient. Alternatively, a battery of tests designed to identify any of several mutations known to result in MM/LGMD2B may be utilized to screen individuals without a defined familial genotype. The analysis can be carried out on any genomic DNA derived from the patient, typically from a blood sample.

Instead of basing the diagnosis on analysis of the genomic DNA of a patient, one could seek evidence of the mutation in the level or nature of the relevant expression products. Well-known techniques for analyzing expression include mRNA-based methods, such as Northern blots and *in situ* hybridization (using a nucleic acid probe derived from the relevant cDNA), and quantitative PCR (as described in St-Jacques et al., 1994, *Endocrinology* 134:2645-57). One could also employ polypeptide based methods, including the use of antibodies specific for the polypeptide of interest. These techniques permit quantitation of the amount of expression of a given gene in the tissue of interest, at least relative to positive and negative controls. One would expect an individual who is heterozygous for a genetic defect affecting the level of expression of

dysferlin to show up to a 50% loss of expression of this gene in such a hybridization or antibody-based assay. An antibody specific for the carboxy terminal end would be likely to pick up (by failure to bind to) most or all frameshift and premature termination signal mutations, as well as deletions of the carboxy terminal sequence. Use of a battery of monoclonal antibodies specific for different epitopes of dysferlin would be useful for rapidly screening cells to detect those expressing mutant forms of dysferlin (i.e., cells which bind to some dysferlin-specific monoclonal antibodies, but not to others), or for quantifying the level of dysferlin on the surface of cells. One could also use a protein truncation assay (Heim et al., 1994, *Nature Genetics* 8:218-19) to screen for any genetic defect which results in the production of a truncated polypeptide instead of the wild type protein.

Use of immunodetection to identify normal and disease-associated dysferlin

In the following example, immunodetection methods are used to demonstrate a detectable difference in muscles homogenates between normal and disease-associated dysferlin alleles.

Frozen muscle samples (quadriceps) were homogenized in ten volumes of SDS-PAGE sample buffer and boiled for 5 minutes. The final loading volume of SDS-PAGE was adjusted after densitometric measurements (NIH Image) of myosin heavy chain on the Coomassie blue stained gels. Studies were performed on six MM, two LGMD-2B, and three normal muscle samples.

Immunocytochemistry was performed on 8 micron cryostat sections of the muscle that were fixed in 100% cold acetone for 5 minutes and preincubated with PBS containing 1% BSA, 5% heat-inactivated goat serum and 0.2% Triton®X-100. The sections were incubated with

primary antibodies overnight at 4°C and fluorescein-labeled secondary (TAGO Immunologicals) for 30 minutes at room temperature. The primary antibodies were applied in two double staining combinations: SalI-1 anti-dysferlin and anti-dystrophin antibodies, and SalI-2 anti-dysferlin and anti-δ-sarcoglycan antibodies. The sections were mounted in SlowFade (Molecular Probes).

The 230 kDA antigen was absent in samples from all five MM patient in immunoblot assays. All five patients had normal patterns of dystrophin expression. Genetic analysis of the dysferlin gene in the patients predicted that at least two of the five MM patients should have no full-length protein. Two of the other three patients had mutations in at least one allele that are predicted to eliminate normal dysferlin expression. In all five patients, absence of dysferlin immuno-staining was documented with at least two other anti-dysferlin anti-sera.

Immunostaining of dysferlin, dystrophin and δ-sarcoglycan proteins demonstrated distinct membrane-associated positivity for each protein in normal muscle. By contrast, in both MM and LGMD-2B muscle the dysferlin protein was absent, while the dystrophin and δ-sarcoglycan proteins appeared normal.

Therapeutic Treatment

A patient with MM/LGMD2B, or an individual genetically susceptible to contracting one or both of these diseases, can be treated by supplying dysferlin therapeutic agents of the present invention. Dysferlin therapeutic agents include a DNA or a subgenomic polynucleotide coding for a functional dysferlin protein. A DNA (e.g., a cDNA) is prepared which encodes the wild type form of the gene operably linked to expression control elements (e.g., promoter and enhancer) that

induce expression in skeletal muscle cells or any other affected cells. The DNA may be incorporated into a vector appropriate for transforming the cells, such as a retrovirus, adenovirus, or adeno-associated virus. One of the many other known types of techniques for introducing DNA into cells *in vivo* may be used (e.g., liposomes). Particularly useful would be naked DNA techniques, since naked DNA is known to be readily taken up by skeletal muscle cells upon injection into muscle. Wildtype dysferlin protein can also be administered to an individual who either expresses mutant dysferlin protein or expresses an inadequate amount of dysferlin protein, *e.g.*, a MM/LGMD2B patient.

Administration of the dysferlin therapeutic agents of the invention can include local or systemic administration, including injection, oral administration, particle gun, or catheterized administration, and topical administration. Various methods can be used to administer the therapeutic dysferlin composition directly to a specific site in the body. For example, a specific muscle can be located and the therapeutic dysferlin composition injected several times in several different locations within the body of the muscle. The therapeutic dysferlin composition can be directly administered to the surface of the muscle, for example, by topical application of the composition. X-ray imaging can be used to assist in certain of the above delivery methods. Combination therapeutic agents, including a dysferlin protein or polypeptide or a subgenomic dysferlin polynucleotide and other therapeutic agents, can be administered simultaneously or sequentially.

Receptor-mediated targeted delivery of therapeutic compositions containing dysferlin subgenomic polynucleotides to specific tissues can also be used. Receptor-mediated DNA delivery techniques are described

in, for example, Findeis et al. (1993), *Trends in Biotechnol. 11*, 202-05; Chiou et al. (1994), Gene Therapeutics: Methods and Applications of Direct Gene Transfer (J.A. Wolff, ed.); Wu & Wu (1988), *J. Biol. Chem. 263*, 621-24; Wu et al. (1994), *J. Biol. Chem. 269*, 542-46; Zenke et al. (1990), *Proc. Natl. Acad. Sci. U.S.A. 87*, 3655-59; Wu et al. (1991), *J. Biol. Chem. 266*, 338-42.

Alternatively, a dysferlin therapeutic composition can be introduced into human cells *ex vivo*, and the cells then implanted into the human. Cells can be removed from a variety of locations including, for example, from a selected muscle. The removed cells can then be contacted with the dysferlin therapeutic composition utilizing any of the above-described techniques, followed by the return of the cells to the human, preferably to or within the vicinity of a muscle. The above-described methods can additionally comprise the steps of depleting fibroblasts or other contaminating non-muscle cells subsequent to removing muscle cells from a human.

Both the dose of the dysferlin composition and the means of administration can be determined based on the specific qualities of the therapeutic composition, the condition, age, and weight of the patient, the progression of the disease, and other relevant factors. If the composition contains dysferlin protein or polypeptide, effective dosages of the composition are in the range of about 1 μg to about 100 mg/kg of patient body weight, e.g., about 50 μg to about 50 mg/kg of patient body weight, e.g., about 500 μg to about 5 mg/kg of patient body weight.

Therapeutic compositions containing dysferlin subgenomic polynucleotides can be administered in a range of about 0.1 μg to about 10 mg of DNA/dose for local administration in a gene therapy protocol. Concentration

ranges of about 0.1 μg to about 10 mg, e.g., about 1 μg to about 1 mg, e.g., about 10 μg to about 100 μg of DNA can also be used during a gene therapy protocol. Factors such as method of action and efficacy of transformation and expression are considerations that will effect the dosage required for ultimate efficacy of the dysferlin subgenomic polynucleotides. Where greater expression is desired over a larger area of tissue, larger amounts of dysferlin subgenomic polynucleotides or the same amounts readministered in a successive protocol of administrations, or several administrations to different adjacent or close tissue portions of for example, a muscle site, may be required to effect a positive therapeutic outcome. In all cases, routine experimentation in clinical trials will determine specific ranges for optimal therapeutic effect.

Animal Model

A line of transgenic animals (e.g., mice, rats, guinea pigs, hamsters, rabbits, or other mammals) can be produced bearing a transgene encoding a defective form of dysferlin. Standard methods of generating such transgenic animals would be used, e.g., as described below.

Alternatively, standard methods of producing null (i.e., knockout) mice could be used to generate a mouse which bears one defective and one wild type allele encoding dysferlin. If desired, two such heterozygous mice could be crossed to produce offspring which are homozygous for the mutant allele. The homozygous mutant offspring would be expected to have a phenotype comparable to the human MM and/or LGMD2B phenotype, and so serve as models for the human disease.

For example, in one embodiment, dysferlin mutations are introduced into a dysferlin gene of a cell, e.g., a

fertilized oocyte or an embryonic stem cell. Such cells can then be used to create non-human transgenic animals in which exogenous altered (e.g., mutated) dysferlin sequences have been introduced into their genome or homologously recombinant animals in which endogenous dysferlin nucleic acid sequences have been altered. Such animals are useful for studying the function and/or activity of dysferlin and for identifying and/or evaluating modulators of dysferlin function. As used herein, a "transgenic animal" is a non-human animal, preferably a mammal, more preferably a rodent such as a rat or mouse, in which one or more of the cells of the animal includes a transgene. Other examples of transgenic animals include non-human primates, sheep, dogs, cows, goats, chickens, amphibians, etc. A transgene is exogenous DNA which is integrated into the genome of a cell from which a transgenic animal develops and which remains in the genome of the mature animal, thereby directing the expression of an encoded gene product in one or more cell types or tissues of the transgenic animal. As used herein, an "homologously recombinant animal" is a non-human animal, preferably a mammal, more preferably a mouse, in which an endogenous dysferlin gene has been altered by homologous recombination between the endogenous gene and an exogenous DNA molecule introduced into a cell of the animal, e.g., an embryonic cell of the animal, prior to completed development of the animal.

A transgenic animal of the invention can be created by introducing a nucleic acid encoding a dysferlin mutation into the male pronuclei of a fertilized oocyte, e.g., by microinjection or retroviral infection, and allowing the oocyte to develop in a pseudopregnant female foster animal. A dysferlin cDNA sequence e.g., that of (SEQ ID NO:1 or SEQ ID NO:3) can be introduced as a

transgene into the genome of a non-human animal. Alternatively, a nonhuman homologue of the human dysferlin gene can be isolated based on hybridization to the human dysferlin sequence (e.g., cDNA) and used as a transgene. Intronic sequences and polyadenylation signals can also be included in the transgene to increase the efficiency of expression of the transgene. Methods for generating transgenic animals via embryo manipulation and microinjection, particularly animals such as mice, have become conventional in the art and are described, for example, in U.S. Patent Nos. 4,736,866 and 4,870,009, U.S. Patent No. 4,873,191 and in Hogan, *Manipulating the Mouse Embryo*, (Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1986). Similar methods are used for production of other transgenic animals. A transgenic founder animal can be identified based upon the presence of the mutant dysferlin transgene in its genome and/or expression of the mutant dysferlin mRNA in tissues or cells of the animals. A transgenic founder animal can then be used to breed additional animals carrying the transgene. Moreover, transgenic animals carrying a transgene encoding a mutant dysferlin can further be bred to other transgenic animals carrying other transgenes.

To create an homologously recombinant animal, a vector is prepared which contains at least a portion of a dysferlin gene into which a deletion, addition or substitution has been introduced to thereby alter a dysferlin gene. In a preferred embodiment, the vector is designed such that, upon homologous recombination, the endogenous dysferlin gene is functionally disrupted (i.e., no longer encodes a functional protein; also referred to as a "knock out" vector). Alternatively, the vector can be designed such that, upon homologous recombination, the endogenous dysferlin gene is mutated

or otherwise altered (e.g., contains one of the mutations described in Table 2). In the homologous recombination vector, the altered portion of the dysferlin sequence is flanked at its 5' and 3' ends by additional nucleic acid of the dysferlin gene to allow for homologous recombination to occur between the exogenous dysferlin nucleic acid sequence carried by the vector and an endogenous dysferlin gene in an embryonic stem cell. The additional flanking dysferlin nucleic acid is of sufficient length for successful homologous recombination with the endogenous gene. Typically, several kilobases of flanking DNA (both at the 5' and 3' ends) are included in the vector (*see, e.g.*, Thomas and Capecchi (1987) *Cell* 51:503 for a description of homologous recombination vectors). The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced dysferlin sequence has homologously recombined with the endogenous dysferlin gene are selected (*see, e.g.*, Li et al. (1992) *Cell* 69:915). The selected cells are then injected into a blastocyst of an animal (e.g., a mouse) to form aggregation chimeras (*see, e.g.*, Bradley in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, Robertson, ed. (IRL, Oxford, 1987) pp. 113-152). A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term. Progeny harboring the homologously recombined DNA in their germ cells can be used to breed animals in which all cells of the animal contain the homologously recombined DNA by germline transmission of the transgene. Methods for constructing homologous recombination vectors and homologous recombinant animals are described further in Bradley (1991) *Current Opinion in Bio/Technology* 2:823-829 and in PCT Publication Nos. WO 90/11354, WO 91/01140, WO 92/0968, and WO 93/04169.

Other Embodiments

It is to be understood that while the invention has been described in conjunction with the detailed description thereof, the foregoing description is intended to illustrate and not limit the scope of the invention, which is defined by the scope of the appended claims. Other aspects, advantages, and modifications are within the scope of the following claims.

What is claimed is:

1. An isolated DNA comprising a nucleotide sequence which hybridizes under stringent hybridization conditions to SEQ ID NO:3, or a complement thereof.

2. The isolated DNA of claim 1, wherein the nucleotide sequence is SEQ ID NO:117.

3. An isolated DNA comprising a nucleotide sequence selected from the group consisting of SEQ ID NOs:4-12.

4. The isolated DNA of claim 3, comprising the sequence of SEQ ID NO:13, SEQ ID NO:14, SEQ ID NO:15, SEQ ID NO:16, SEQ ID NO:17, SEQ ID NO:18, SEQ ID NO:19, SEQ ID NO:20, or SEQ ID NO:21.

5. An isolated DNA comprising a nucleotide sequence selected from the group consisting of SEQ ID NOS:22-30.

6. A single stranded oligonucleotide of 14-50 nucleotides in length having a nucleotide sequence identical to a portion of SEQ ID NO:3, or a complement thereof.

7. A pair of PCR primers consisting of:

(a) a first single stranded oligonucleotide consisting of 14-50 contiguous nucleotides that are identical to a portion of SEQ ID NO:117; and

(b) a second single stranded oligonucleotide consisting of 14-50 contiguous nucleotides that are identical to a portion of SEQ ID NO:117, wherein the sequence of at least one of the oligonucleotides is identical to a portion of a strand of SEQ ID NO:3, and the first oligonucleotide is not complementary to the second oligonucleotide.

8. A pair of single-stranded oligonucleotides, wherein both oligonucleotides are selected from the group consisting of SEQ ID NOS:130-231, SEQ ID NO:110, and SEQ ID NO:112 and the oligonucleotides are different from each other.

9. An isolated DNA comprising a nucleotide sequence that encodes a polypeptide that shares at least 70% sequence identity with SEQ ID NO:2, or a complement of the nucleotide sequence.

10. The isolated DNA of claim 9, wherein the polypeptide comprises the sequence of SEQ ID NO:2.

11. An isolated DNA comprising a nucleotide sequence which hybridizes under stringent hybridization conditions to a nucleic acid having a sequence selected from the group consisting of SEQ ID NOs:31-79 and 90-100.

12. A single stranded oligonucleotide of 14-50 nucleotides in length comprising a nucleotide sequence which is identical to a portion of a nucleic acid selected from the group consisting of SEQ ID NOs:31-79 and 90-100, or a complement of the nucleotide sequence.

13. The oligonucleotide of claim 12, wherein the portion includes an intronic sequence.

14. A pair of PCR primers consisting of:

(a) a first single-stranded oligonucleotide consisting of 14-50 contiguous nucleotides that are identical to a portion of a sense strand of a nucleic acid selected from the group consisting of SEQ ID NOs:31-85; and

(b) a second single stranded oligonucleotide consisting of 14-50 contiguous nucleotides that are identical to a portion of the antisense strand of a nucleic acid selected from the group consisting of SEQ ID NOs:31-85, wherein the sequence of at least one of the oligonucleotides comprises a sequence identical to a portion of a nucleic acid selected from SEQ ID NOs: 31-79 and 90-100, and wherein the first oligonucleotide is not complementary to the second oligonucleotide.

15. A pair of single-stranded oligonucleotides selected from the group consisting of SEQ ID NOs:101-116, SEQ ID NOs:184-185, SEQ ID NOs:188-191, SEQ ID NOs:210-213, and SEQ ID NOs:216-217.

16. A vector comprising the isolated DNA of claim 1.

17. A substantially pure polypeptide comprising an amino acid sequence sharing at least 70% sequence identity with SEQ ID NO:2.

18. The substantially pure polypeptide of claim 17, wherein the polypeptide comprises an amino acid sequence identical to that of a naturally occurring polypeptide.

19. The substantially pure polypeptide of claim 18, wherein the amino acid sequence comprises the sequence of SEQ ID NO:2.

20. A substantially pure polypeptide comprising an amino acid sequence identical to the amino acid sequence of amino acid residues 1-500, 501-1000, 1001-1500, or 1501-2080 of SEQ ID NO:2.

21. A substantially pure polypeptide comprising the amino acid sequence of SEQ ID NO:86, SEQ ID NO:87, SEQ ID NO:88 or SEQ ID NO:89.

22. A substantially pure polypeptide selected from the group consisting of amino acids 253-403 of SEQ ID NO:2, amino acids 624-865 of SEQ ID NO:2, and amino acids 1664-1786 of SEQ ID NO:2.

23. A fusion protein comprising a polypeptide of claim 22.

24. An antibody that specifically binds to the polypeptide of claim 22.

25. An antibody that binds specifically to the polypeptide of claim 17.

26. A cell comprising the isolated DNA of claim 1.

27. A non-human mammal, the genomic DNA of which bears a transgene, wherein the transgene comprises the isolated DNA of claim 1.

28. A transgenic non-human mammal having a transgene disrupting or interfering with the expression of a dysferlin gene.

29. A method of decreasing the symptoms of muscular dystrophy in a mammal, the method comprising introducing into a cell of said mammal the isolated DNA of claim 1.

30. A method of decreasing the symptoms of muscular dystrophy in a mammal, the method comprising introducing

into a cell of said mammal the vector of claim 16, the vector being an expression vector.

31. A method of decreasing the symptoms of muscular dystrophy in a mammal, the method comprising introducing into a cell of said mammal the protein of claim 17.

32. A method for identifying a patient, a fetus, or a pre-embryo at risk for having a dysferlin-related disorder, the method comprising:

(a) obtaining a sample of genomic DNA from the patient, fetus, or pre-embryo; and

(b) determining whether the sample contains a mutation in a dysferlin gene, wherein a patient, a fetus, or a pre-embryo having a mutation in a dysferlin gene is at risk for having a dysferlin-related disorder.

33. The method of claim 32, comprising:

(a) treating the sample of genomic DNA with a restriction enzyme specific for a particular restriction enzyme site; and

(b) detecting the presence or absence of the particular restriction enzyme site in the sample of genomic DNA as an indication of the presence or absence of a particular mutation in the genomic DNA.

34. The method of claim 33, wherein the restriction enzyme is selected from the group consisting of Pst I, Fnu4H I, BamH I, BstY I, Ava II, HinP I, Fsp I, Mbo II, ScrF I, BstN I, Mae I, Bfa I, Dde I, Bpm I, Ban II, Ava II, and Sau96 I.

35. The method of claim 32, comprising subjecting the sample to polymerase chain reaction (PCR).

36. The method of claim 32, comprising:

(a) contacting a single stranded oligonucleotide with the sample of genomic DNA; and

(c) detecting hybridization or lack thereof between the single stranded oligonucleotide and the genomic DNA, as an indication of the presence or absence of a mutation in the genomic DNA.

37. A method for identifying a patient, a fetus, or a pre-embryo at risk for having a dysferlin-related disorder, said method comprising:

(a) providing a sample comprising dysferlin mRNA from the patient, fetus, or pre-embryo; and

(b) determining whether the dysferlin mRNA contains a mutation, wherein a patient, a fetus, or a pre-embryo having a dysferlin mRNA containing a mutation is at risk for having a dysferlin-related disorder.

38. The method of claim 37, wherein the presence or absence of the mutation is detected by Northern blot.

39. The method of claim 37, wherein the method includes the step of subjecting the sample to polymerase chain reaction (PCR).

40. A method for detecting the absence of a mutation in a dysferlin protein of a patient, a fetus, or a pre-embryo, the method comprising:

(a) providing a sample comprising a dysferlin protein of the patient, fetus, or pre-embryo;

(b) contacting the sample with the antibody of claim 22; and

(c) detecting binding of the antibody to dysferlin protein in the sample, if any, wherein binding indicates a normal dysferlin protein.

41. An isolated DNA comprising a nucleotide sequence that is identical to the sequence of amino acid residues 3501-3520 of SEQ ID NO:1, 3737-3756 of SEQ ID NO:1, 3842-3861 of SEQ ID NO:1, 5114-5139 of SEQ ID NO:1, or 5239-5255 of SEQ ID NO:1.

42. An isolated DNA comprising a nucleotide sequence selected from the group consisting of

3501-3520 of SEQ ID NO:1, wherein nucleotide G at 3510 is A;

3737-3756 of SEQ ID NO:1, wherein nucleotide G at 3746 is deleted;

3842-3861 of SEQ ID NO:1, wherein nucleotide C at 3851 is T;

5114-5139 of SEQ ID NO:1, wherein nucleotide C at 5122 and nucleotide A at 5123 are deleted;

5239-5255 of SEQ ID NO:1, wherein nucleotide G at 5245 is deleted and nucleotide G at 5249 is C; and

5239-5255 of SEQ ID NO:1, wherein nucleotide G at 5245 is C and nucleotide G at 5249 is deleted.

43. An isolated nucleic acid comprising a nucleotide sequence which hybridizes under stringent hybridization conditions to nucleic acids 3284-3720 of SEQ ID NO:232, or the complement of said nucleotide sequence.

44. An isolated nucleic acid comprising a nucleotide sequence identical to the sequence of nucleotides 3284-3720 of SEQ ID NO:232, or a complement of said nucleotide sequence.

45. The isolated nucleic acid of claim 44, wherein the nucleotide sequence comprises the sequence of SEQ ID NO:232 or the complement of SEQ ID NO:232.

46. An isolated polypeptide comprising:

a) at least 15 contiguous amino acids of the polypeptide comprising amino acids 1-24 of SEQ ID NO:233,

b) a naturally occuring allelic variant of a polypeptide comprising amino acids 1-24 of SEQ ID NO:233, or

c) an amino acid sequence which is encoded by a nucleic acid molecule which hybridizes under stringent conditions to nucleotides 3284-3720 of SEQ ID NO:232.

47. The polypeptide of claim 46, wherein the polypeptide comprises SEQ ID NO:233.

48. A vector comprising the nucleic acid of claim 44.

49. A cell comprising the vector of claim 48.

50. A method of making a polypeptide, the method comprising culturing the cell of claim 49.

51. An antibody which specifically binds to a polypeptide of claim 46.

52. The antibody of claim 51, wherein the antibody binds to a polypeptide selected from the group comprising amino acids 253-403 of SEQ ID NO:233, amino acids 624-865 of SEQ ID NO:233, and amino acids 1664-1786 of SEQ ID NO:233.

53. The antibody of claim 51, wherein the antibody is a monclonal antibody.

54. The antibody of claim 51, wherein the antibody is a polyclonal antibody.

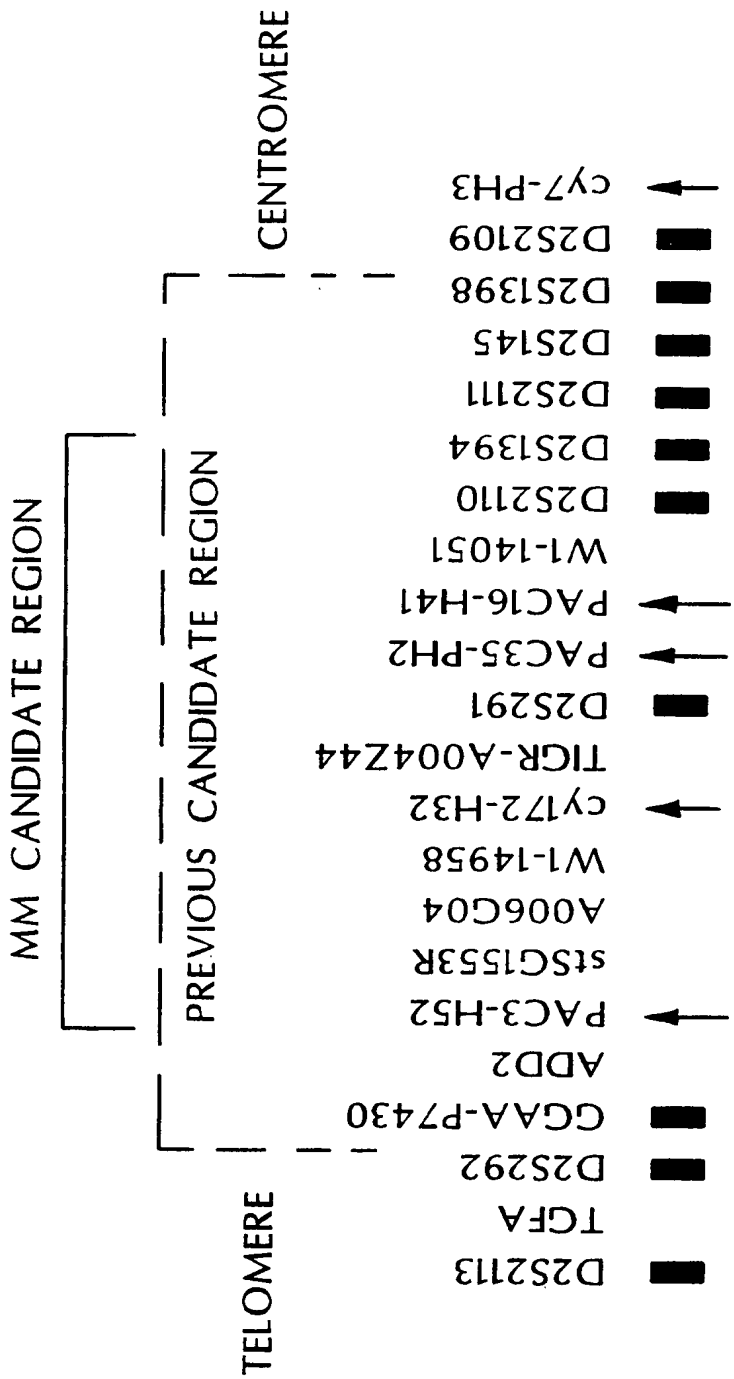

FIG. 1A

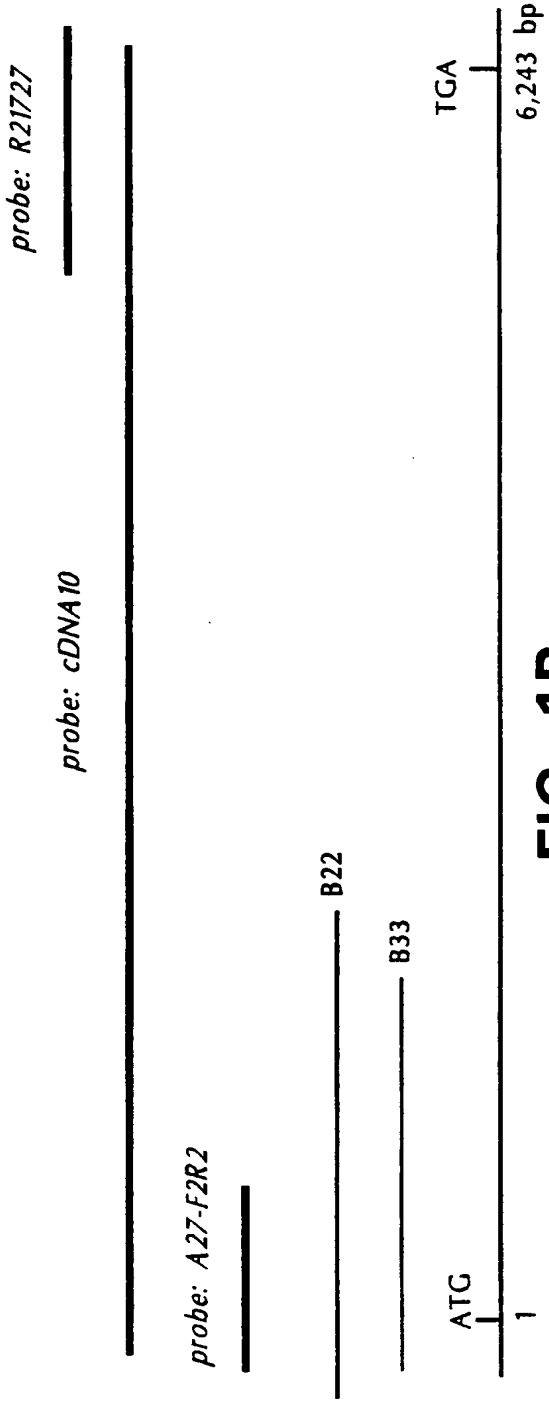

FIG. 1B

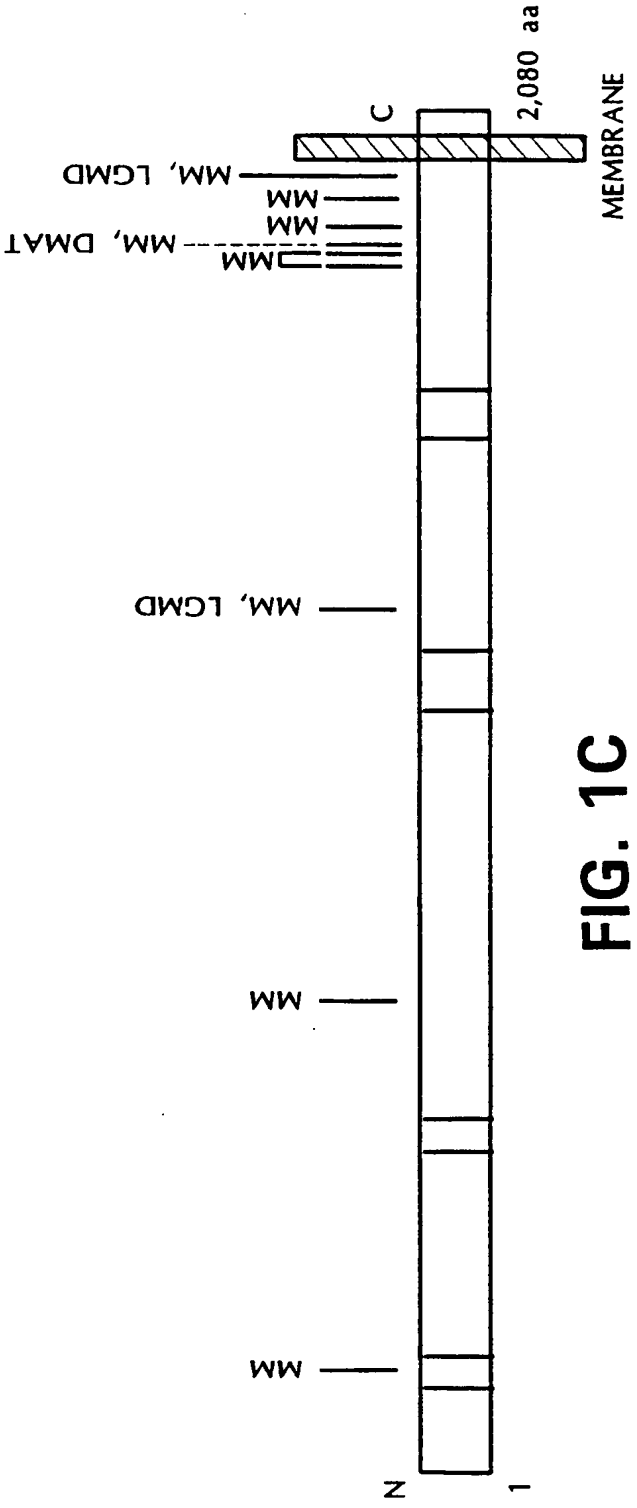

FIG. 1C

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   1 MLRVHILYAE NVHTPDTDIS DAYCSAVFAG VKKRTKVIKN SVNPVWNEGF
  51 EWDLKGIPLD CGSELHVVVK DHETMGRNRE LGEAKVPLRE VLATPSLSAS
 101 FNAPLLDTKK QPTGASLVLQ VSYTPLPGAV PLFPPPTPLE PSPTLPDLDV
 151 VADTGGEEDT EDQGLTGDEA EPFLDQSGGP GAPTTPRKLP SRPPPHYPGI
 201 KRKRSAPTSR KLLSDKPQDF CIRVQVIEGR QLPGVNIKPV VKVTAAGQTK
 251 RTRIHKGNSP LFNETLFFNL FDSPGELFDE PIFITVVDSR SLRTDALLGE
 301 FRMDVGTIYR EPRHAYLRKW LLLSDPDDFS AGARGYLKTS LCVLGPGDEA
 351 PLERKDPSED KEDIESNLLR PTGVALRGAH FCLKVFRAED LPQMDDAVMD
 401 NVKQIFGFES NKKNLVDPFV EVSFAGKQLC SKILEKTINP QWNQNITLPA
 451 MFPSMCEKVR IEIIDWDRLT RNDIVATTYL SMSKISAPGG EIEEEPAGAV
 501 KPSKASDLDD YLGFLPTTFG PCYINLYGSP EFTGFPDPYT ELNTGKGEGV
 551 AYRGRLLLSL ETKLVEHSEQ KVEDLPADDI LRVEKYLRRR KYSLFAAFYS
 601 ATMLQDVDDA IQFEVSIGNY GNKFDMTCLP LASTTQYSRA VFDGCHYYYL
 651 PWGNVKPVVV LSSYWEDISH RIETQNQLLG IADRLEAGLE QVHLALKAQC
 701 STEDVDSLVA QLTDELIAGC SQPLGDIHET PSATHLDQYL YQLRTHHLSQ
 751 ITEAALALKL GHSELPAALE QAEDWLLRLR ALAEEPQNSL PDIVIWMLQG
 801 DKRVAYQRVP AHQVLFSRRG ANYCGKNCGK LQTIFLKYPM EKVPGARMPV
 851 QIRVKLWFGL SVDEKEFNQF AEGKLSVFAE TYENETKLAL VGNWGTTGLT
 901 YPKFSDVTGK IKLPKDSFRP SAGWTWAGDW FVCPEKTLLH DMDAGHLSFV
 951 EEVFENQTRL PGGQWIYMSD NYTDVNGEKV LPKDDIECPL GWKWEDEEWS
1001 TDLNRAVDEQ GWEYSITIPP ERKPKHWVPA EKMYYTERRR RWVRLRRRDL
1051 SQMEALKRHR QAEAEGEGWE YASLPGWKFH LEYRKTDAFR RRRWRRRMEP
1101 LEKTGPAAVF ALEGALGGVM DDKSEDSMSV STLSFGVNRP TISCIFDYGN
1151 RYHLRCYMYQ ARDLAAMDKD SFSDPYAIVS FLHQSQKTVV VKNTLNPTWD
1201 QTLIFYEIEI FGEPATVAEQ PPSIVVELYD HDTYGADEFM GRCICQPSLE
1251 RMPRLAWFPL TRGSQPSGEL LASFELIQRE KPAIHHIPGF EVQETSRILD
1301 ESEDTDLPYP PPQREANIYM VPQNIKPALQ RTAIEILAWG LRNMKSYQLA
1351 NISSPSLVVE CGGQTVQSCV IRNLRKNPNF DICTLFMEVM LPREELYCPP
1401 ITVKVIDNRQ FGRRPVVGQC TIRSLESFLC DPYSAESPSP QGGPDDVSLL
1451 SPGEDVLIDI DDKEPLIPIQ EEEFIDWWSK FFASIGEREK CGSYLEKDFD
1501 TLKVYDTQLE NVEAFEGLSD FCNTFKLYRG KTQEETEDPS VIGEFKGLFK
1551 IYPLPEDPAI PMPPRQFHQL AAQGPQECLV RIVIVEAEGL QPKDPNGKCD
1601 PYIKISLGKK SVSDQDNYIP CTLEPVFGKM FELTCTLPLE KDLKITLYDY
1651 DLLSKDEKIG ETVVDLENRL LSKFGARCGL PQTYCVSGPN QWRDQLRPSQ
1701 LLHLFCQQHR VKAPVYRTDR VMFQDKEYSI EEIEAGRIPN PHLGPVEERL
1751 ALHVLQQQGL VPEHVESRPL YSPLQPDIEQ GKLQMWVDLF PKALGRPGPP
1801 FNITPRRARR FFLRCIIWNT RDVILDDLSL TGEKMSDIYV KGWMIGFEEH
1851 KQKTDVHYRS LGGEGNFNWR FIFPFDYLPA EQVCTIAKKD AFWRLDKTES
1901 KIPARVVFQI WDNDKFSFDD FLGSLQLDLN RMPKPAKTAK KCSLDQLDDA
1951 FHPEWFVSLF EQKTVKGWWP CVAEEGEKKI LAGKLEMTLE IVAESEHEER
2001 PAGQGRDEPN MNPKLEDPRR PDTSFLWFTS PYKTMKFILW RRFRWAIILF
2051 IILFILLLFL AIFIYAFPNY AAMKLQKEES
```

(SEQ ID NO:2)

FIG. 2

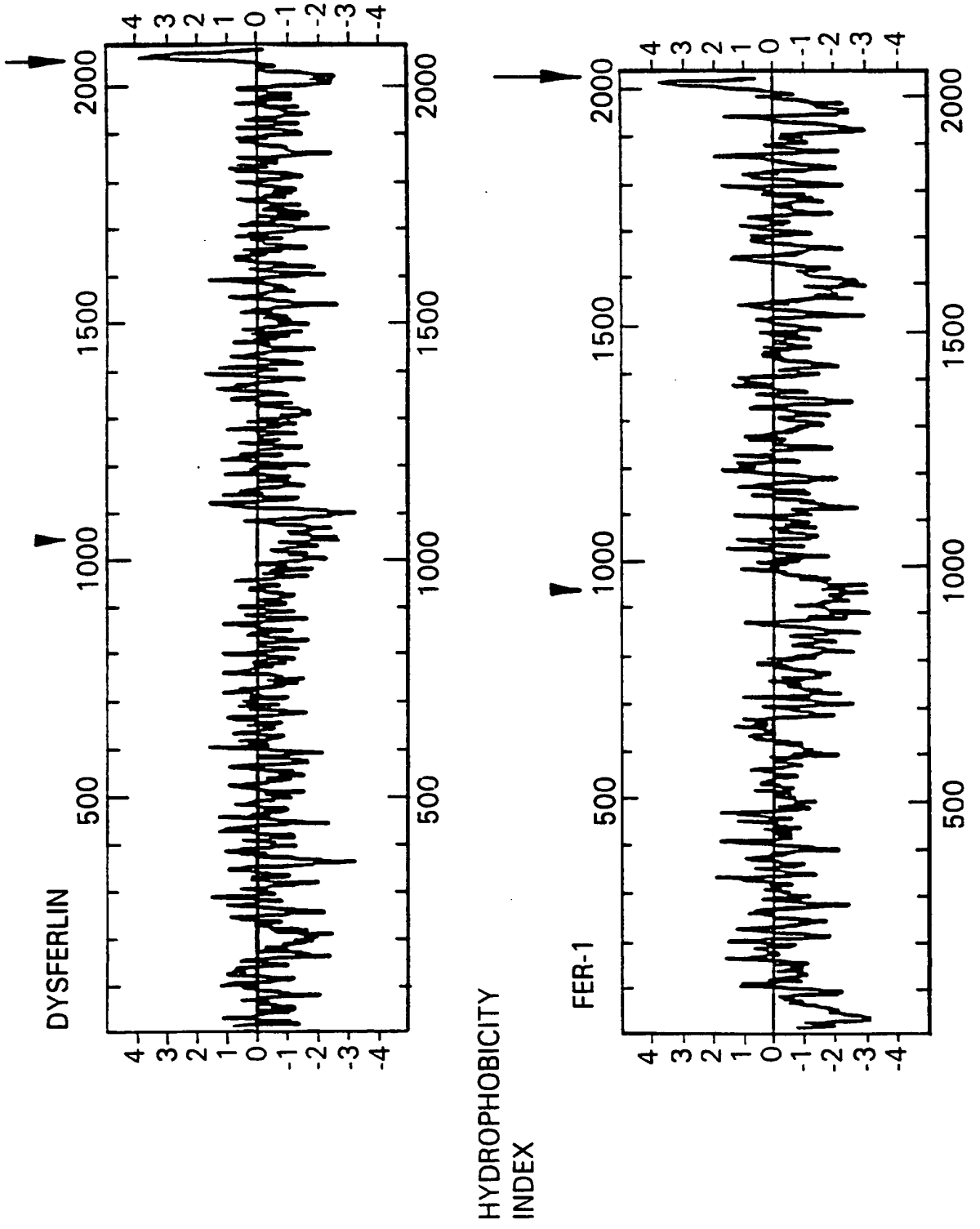

FIG. 3

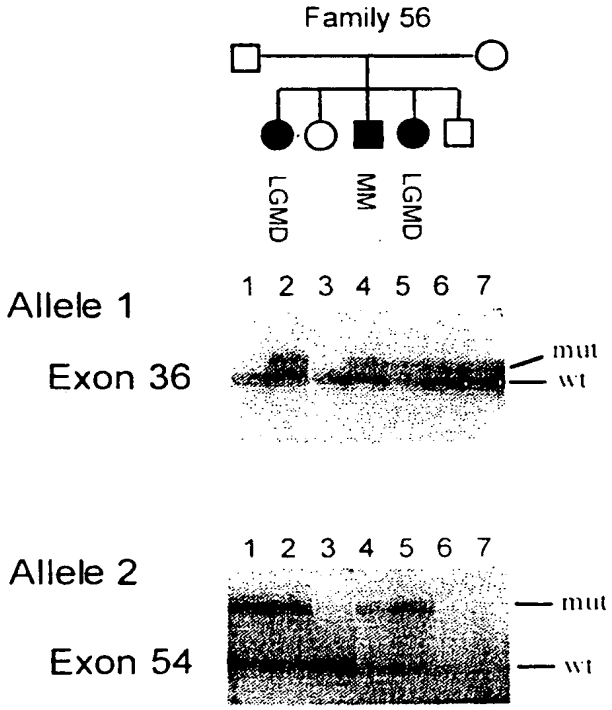

FIG. 4

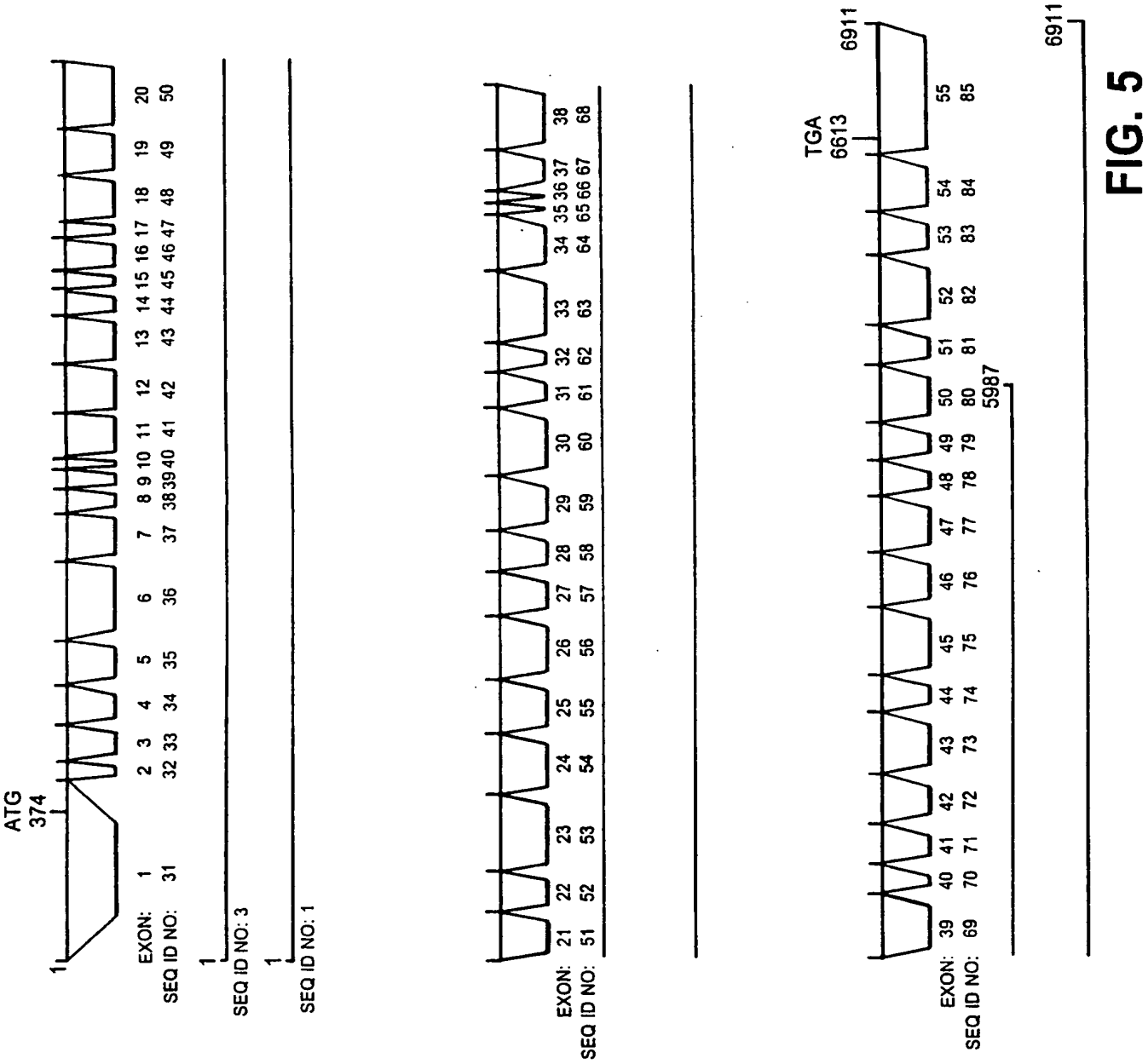

FIG. 5

```
1/1                                31/11                                61/21
TCC TGG TTC AAG CGA TTC TCT GGC CTC AGC CTC CCG AGT AGC TGG GAT TAC AGG CAT GCT CCA CCA AGC CCG GGT AAT TTT GTA TTT TTA
S  W  F  K  R  F  S  G  L  S  L  P  S  S  W  D  Y  R  H  A  P  P  S  P  G  N  F  V  F  L
91/31                              121/41                               151/51
ATA GAG ACG GGG TTT TGC CAT GTT GGT CAG GCT GGT CTC GAA CTC CTG ACC TCA GGT GAT CTG CCC ACC TTG GCC TCC CAA CGT GCT GAG
I  E  T  G  F  C  H  V  G  Q  A  G  L  E  L  L  T  S  G  D  L  P  T  L  A  S  Q  R  A  E
181/61                             211/71                               241/81
ATT ACA GGC ATG AGT CAC TGT GCC CGG CAG AGA TGG TCT AAT TCA TAT GAA AGA ACT CTG AAA AAA GTA GAA AGT GAT TTT CTA AAA TAA
I  T  G  M  S  H  C  A  R  Q  R  W  S  N  S  I  E  R  T  L  K  K  V  E  S  D  F  L  K  *
271/91                             301/101                              331/111
GGT ACA AAT AAT TAA TGT AAG CAT AAT CAC CTA ACC TTG TGG AAT TTT TTT TTT TTG AGA AGC AAA TTG CAA ATT TGT GAT AGA TCT AAA
G  T  N  N  *  C  K  H  N  H  L  T  L  W  N  F  F  F  L  R  S  K  L  Q  I  C  D  R  S  K
361/121                            391/131                              421/141
GGA GAT TGA CTA AGA GGG TGA CCA TCT GGA AAT GAC GTC ATG TGA GAA TGG TTA AAG ATG CTC GGG AGA TTG AGC CTA GAG AAA GGA AGA
G  D  *  L  R  G  *  P  S  G  N  D  V  M  *  E  W  L  K  M  L  G  R  L  S  L  E  K  G  R
451/151                            481/161                              511/171
TTT GTG AAC CCA GGA GGC AGA GGT AGA GAT CCA GGA GAG ggc ggc gtg atg gat gac aag agt gaa gat tcc atg tcc gtc tcc acc ttg
F  V  N  P  G  G  R  G  R  D  P  G  E  G  G  V  M  D  D  K  S  E  D  S  M  S  V  S  T  L
541/181                            571/191                              601/201
agc tcc ggt gtg aac aga ccc acg att tcc tgc ata ttc gac tat ggg aac cgc tac cat cca cgc tgc tac atg tac cag gcc cgg gac
S  F  G  V  N  R  P  T  I  S  C  I  F  D  Y  G  N  R  Y  H  L  R  C  Y  M  Y  Q  A  R  D
631/211                            661/221                              691/231
ctg gct gcg atg gac aag gac tct ttt tct gat ccc tat gcc atc gtc ttc ctg cac cag agc cag aag acg gtg gtg aag aac
L  A  A  M  D  K  D  S  F  S  D  P  Y  A  I  V  S  F  L  H  Q  S  Q  K  T  V  V  K  N
721/241                            751/251                              781/261
acc ctt aac ccc acc tgg gac cag acg ctc atc ttc tac gag atc gag atc ttt ggc gag ccg gcc aca gtt gct gag caa ccg ccc agc
T  L  N  P  T  W  D  Q  T  L  I  F  Y  E  I  E  I  F  G  E  P  A  T  V  A  E  Q  P  P  S
```

FIG. 6A

```
811/271                                 841/281                                 871/291
att gtg gtg gag ctg tac gac cat gac act tat ggt gca gac gag ttt atg ggt cgc tgc atc tgt caa ccg agt ctg gaa cgg atg cca
 I   V   V   E   L   Y   D   H   D   T   Y   G   A   D   E   F   M   G   R   C   I   C   Q   P   S   L   E   R   M   P
901/301                                 931/311                                 961/321
cgg ctg gcc tgg ttc cca ctg acg agg ggc agc cag ccg tcg ggg gag ctg ctg gcc tct ttt gag ctc atc cag aga gag aag ccg gcc
 R   L   A   W   F   P   L   T   R   G   S   Q   P   S   G   E   L   L   A   S   F   E   L   I   Q   R   E   K   P   A
991/331                                 1021/341                                1051/351
atc cac cat att cct ggt ttt gag gtg cag gag aca tca agg atc ctg gat gag tct gag gac aca gac ctg ccc tac cca cca ccc cag
 I   H   H   I   P   G   F   E   V   Q   E   T   S   R   I   L   D   E   S   E   D   T   D   L   P   Y   P   P   P   Q
1081/361                                1111/371                                1141/381
agg gag gcc aac atc tac atg gtt cct cag aac atc aag cca gcg ctc cag cgt acc gcc atc gag atc ctg gca tgg ggc ctg cgg aac
 R   E   A   N   I   Y   M   V   P   Q   N   I   K   P   A   L   Q   R   T   A   I   E   I   L   A   W   G   L   R   N
1171/391                                1201/401                                1231/411
atg aag agt tac cag ctg gcc aac atc tcc tcc ccc agc ctc gtg gta gag tgt ggg ggc cag acg gtg cag tcc tgt gtc atc agg aac
 M   K   S   Y   Q   L   A   N   I   S   S   P   S   L   V   V   E   C   G   G   Q   T   V   Q   S   C   V   I   R   N
1261/421                                1291/431                                1321/441
ctc cgg aag aac ccc aac ttt gac atc tgc acc ctc ttc atg gaa gtg atg ctg ccc agg gag gag ctc tac tgc ccc ccc atc acc gtc
 L   R   K   N   P   N   F   D   I   C   T   L   F   M   E   V   M   L   P   R   E   E   L   Y   C   P   P   I   T   V
1351/451                                1381/461                                1411/471
aag gtc atc gat aac cgc cag ttt ggc cgc cgg cct gtg gtg ggc cag tgt acc atc cgc tcc ctg gag agc ttc ctg tgt gac ccc tac
 K   V   I   D   N   R   Q   F   G   R   R   P   V   V   G   Q   C   T   I   R   S   L   E   S   F   L   C   D   P   Y
1441/481                                1471/491                                1501/501
tcg gcg gag agt cca tcc cca cag ggt ggc cca gac gat gtg agc cta ctc agt cct ggg gaa gac gtg ctc atc gac att gat gac aag
 S   A   E   S   P   S   P   Q   G   G   P   D   D   V   S   L   L   S   P   G   E   D   V   L   I   D   I   D   D   K
1531/511                                1561/521                                1591/531
gag ccc ctc atc ccc atc cag gag gaa gag ttc atc gat tgg tgg agc aaa ttc ttt gcc tcc ata ggg gag agg gaa aag tgc ggc tcc
 E   P   L   I   P   I   Q   E   E   E   F   I   D   W   W   S   K   F   F   A   S   I   G   E   R   E   K   C   G   S
1621/541                                1651/551                                1681/561
tac ctg gag aag gat ttt gac acc ctg aag gtc tat gac aca cag ctg gag aat gtg gag gcc ttt gag ggc ctg tct gac ttt tgt aac
 Y   L   E   K   D   F   D   T   L   K   V   Y   D   T   Q   L   E   N   V   E   A   F   E   G   L   S   D   F   C   N
```

FIG. 6B

```
1711/571                1741/581                1771/591
acc ttc aag ctg tac cgg ggc aag acg cag gag gag aca gaa gat cca tct gtg att ggt gaa ttt aag ggc ctc ttc aaa att tat ccc
T   F   K   L   Y   R   G   K   T   Q   E   E   T   E   D   P   S   V   I   G   E   F   K   G   L   F   K   I   Y   P
1801/601                1831/611                1861/621
ctc cca gaa gac cca gcc atc ccc atg ccc cca aga cag ttc cac cag ctg gcc gcc cag gga ccc cag gag tgc ttg gtc cgt atc tac
L   P   E   D   P   A   I   P   M   P   P   R   Q   F   H   Q   L   A   A   Q   G   P   Q   E   C   L   V   R   I   Y
1891/631                1921/641                1951/651
att gtc cga gca ttt ggc ctg cag ccc aag gac ccc aat gga aag tgt gat cct tac atc aag atc tcc ata ggg aag aaa tca gtg agt
I   V   R   A   F   G   L   Q   P   K   D   P   N   G   K   C   D   P   Y   I   K   I   S   I   G   K   K   S   V   S
1981/661                2011/671                2041/681
gac cag gat aac tac atc ccc tgc acg ctg gag ccc gta ttt gga aag atg ttc gag ctg acc tgc act ctg cct ctg gag aag gac cta
D   Q   D   N   Y   I   P   C   T   L   E   P   V   F   G   K   M   F   E   L   T   C   T   L   P   L   E   K   D   L
2071/691                2101/701                2131/711
aag atc act ctc tat gac tat gac ctc ctc tcc aag gac gaa aag atc ggt gag acg gtc gtc gac ctg gag aac agg ctg ctg tcc aag
K   I   T   L   Y   D   Y   D   L   L   S   K   D   E   K   I   G   E   T   V   V   D   L   E   N   R   L   L   S   K
2161/721                2191/731                2221/741
ttt ggg gct cgc tgt gga ctc cca cag acc tac tgt gtc tct gga ccg aac cag tgg cgg gac cag ctc cgc ccc tcc cag ctc ctc cac
F   G   A   R   C   G   L   P   Q   T   Y   C   V   S   G   P   N   Q   W   R   D   Q   L   R   P   S   Q   L   L   H
2251/751                2281/761                2311/771
ctc ttc tgc cag cag cat aga gtc aag gca cct gtg tac cgg aca gac cgt gta atg ttt cag gat aaa gaa tat tcc att gaa gag ata
L   F   C   Q   Q   H   R   V   K   A   P   V   Y   R   T   D   R   V   M   F   Q   D   K   E   Y   S   I   E   E   I
2341/781                2371/791                2401/801
gag gct ggc agg atc cca aac cca cac ctg ggc cca gtg gag gag cgt ctg gct ctg cat gtg ctt cag cag cag ggc ctg gtc ccg gag
E   A   G   R   I   P   N   P   H   L   G   P   V   E   E   R   L   A   L   H   V   L   Q   Q   Q   G   L   V   P   E
2431/811                2461/821                2491/831
cac gtg gag tca cgg ccc ctc tac agc ccc ctg cag cca gac atc gag cag ggg aag ctg cag atg tgg gtc gac cta ttt ccg aag gcc
H   V   E   S   R   P   L   Y   S   P   L   Q   P   D   I   E   Q   G   K   L   Q   M   W   V   D   L   F   P   K   A
2521/841                2551/851                2581/861
ctg ggg cgg cct gga cct ccc ttc aac atc acc cca cgg aga gcc aga agg ttt ttc ctg cgt tgt att atc tgg aat acc aga gat gtg
L   G   R   P   G   P   P   F   N   I   T   P   R   R   A   R   R   F   F   L   R   C   I   I   W   N   T   R   D   V
2611/871                2641/881                2671/891
atc ctg gat gac ctg agc ctc acg ggg gag aag atg agc gac att tat gtg aaa ggt tgg atg att ggc ttt gaa gaa cac aag caa aag
I   L   D   D   L   S   L   T   G   E   K   M   S   D   I   Y   V   K   G   W   M   I   G   F   E   E   H   K   Q   K
```

FIG. 6C

```
2701/901                                                  2731/911                                                  2761/921
aca gac gtg cat tat cgt tcc ctg gga ggt gaa ggc aac ttc aac tgg agg ttc att ttc ccc ttc gac tac ctg cca gct gag caa gtc
T   D   V   H   Y   R   S   L   G   G   E   G   N   F   N   W   R   F   I   F   P   F   D   Y   L   P   A   E   Q   V
2791/931                                                  2821/941                                                  2851/951
tgt acc att gcc aag aag gat gcc ttc tgg agg ctg gac aag act gag agc aaa atc cca gca cga gtg gtg ttc cag atc tgg gac aat
C   T   I   A   K   K   D   A   F   W   R   L   D   K   T   E   S   K   I   P   A   R   V   V   F   Q   I   W   D   N
2881/961                                                  2911/971                                                  2941/981
gac aag ttc tcc ttt gat gat ttt ctg ggc tcc ctg cag ctc gat ctc aac cgc atg ccc aag cca gcc aag aca gcc aag aag tgc tcc
D   K   F   S   F   D   D   F   L   G   S   L   Q   L   D   L   N   R   M   P   K   P   A   K   T   A   K   K   C   S
2971/991                                                  3001/1001                                                 3031/1011
ttg gac cag ctg gat gat gct ttc cac cca gaa tgg ttt gtg tcc ctt ttt gag cag aaa aca gtg aag ggc tgg tgg ccc tgt gta gca
L   D   Q   L   D   D   A   F   H   P   E   W   F   V   S   L   F   E   Q   K   T   V   K   G   W   W   P   C   V   A
3061/1021                                                 3091/1031                                                 3121/1041
gaa gag ggt gag aag aaa ata ctg gcg ggc aag ctg gaa atg acc ttg gag att gta gca gag agt gag cat gag gag cgg cct gct ggc
E   E   G   E   K   K   I   L   A   G   K   L   E   M   T   L   E   I   V   A   E   S   E   H   E   E   R   P   A   G
3151/1051                                                 3181/1061                                                 3211/1071
cag ggc cgg gat gag ccc aac atg aac cct aag ctt gag gac cca agg cgc ccc gac acc tcc ttc ctg tgg ttt acc tcc cca tac aag
Q   G   R   D   E   P   N   M   N   P   K   L   E   D   P   R   R   P   D   T   S   F   L   W   F   T   S   P   Y   K
3241/1081                                                 3271/1091                                                 3301/1101
acc atg aag ttc atc ctg tgg cgg cgt ttc cgg tgg gcc atc atc ctc ttc atc atc ctc ttc atc ctg ctg ctg ttc ctg gcc atc ttc
T   M   K   F   I   L   W   R   R   F   R   W   A   I   I   L   F   I   I   L   F   I   L   L   L   F   L   A   I   F
3331/1111                                                 3361/1121                                                 3391/1131
atc tac gcc ttc ccg aac tat gct gcc atg aag ctg gtg aag ccc ttc agc tga gga ctc tcc tgc cct gta gaa ggg gcc gtg ggg tcc
I   Y   A   F   P   N   Y   A   A   M   K   L   V   K   P   F   S   *   G   L   S   C   P   V   E   G   A   V   G   S
3421/1141                                                 3451/1151                                                 3481/1161
cct cca gca tgg gac tgg cct gcc tcc tcc gcc cag ctc ggc gag ctc ctc cag acc tcc tag gcc tga ttg tcc tgc cag ggt ggg cag
P   P   A   W   D   W   P   A   S   S   A   Q   L   G   E   L   L   Q   T   S   *   A   *   L   S   C   Q   G   G   Q
3511/1171                                                 3541/1181                                                 3571/1191
aca gac aga tgg acc ggc cca cac tcc cag agt tgc taa cat gga gct ctg aga tca ccc cac ttc cat cat ttc ctt ctc ccc caa ccc
T   D   R   W   T   G   P   H   S   Q   S   C   *   H   G   A   L   R   S   P   H   F   H   H   F   L   L   P   Q   P
3601/1201                                                 3631/1211                                                 3661/1221
aac gct ttt ttg gat cag ctc aga cat att tca gta taa aac agt tgg aac cac aaa aaa aaa aaa aaa aa  (SEQ ID NO:232)
N   A   F   L   D   Q   L   R   H   I   S   V   *   N   S   W   N   H   K   K   K   K   K       (SEQ ID NO:233)
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FIG. 6D

SEQUENCE LISTING

<110> The General Hospital Corporation

<120> DYSFERLIN, A GENE MUTATED IN DISTAL MYOPATHY AND LIMB GIRDLE MUSCULAR DYSTROPHY

<130> 00786/399WO2

<150> US 60/097,927
<151> 1998-08-25

<160> 233

<170> FastSEQ for Windows Version 3.0

<210> 1
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<212> DNA
<213> Homo sapiens

<220>
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agattacagc tcgacggagc tcgggaaggg cggcgggggt ggaagatgag cagaagcccc     120
tgttctcgga acgccggctg acaagcgggg tgagcgcagg cggggcgggg acccagccta     180
gcccactgga gcagccgggg gtggcccgtt ccccttaag agcaactgct ctaagccagg      240
agccagagat tcgagccggc ctcgcccagc cagccctctc cagcgagggg acccacaagc     300
ggcgcctcgg ccctcccgac ctttccgagc cctctttgcg ccctgggcgc acggggccct     360
acacgcgcca agc atg ctg agg gtc ttc atc ctc tat gcc gag aac gtc         409
                Met Leu Arg Val Phe Ile Leu Tyr Ala Glu Asn Val
                  1               5                  10

cac aca ccc gac acc gac atc agc gat gcc tac tgc tcc gcg gtg ttt      457
His Thr Pro Asp Thr Asp Ile Ser Asp Ala Tyr Cys Ser Ala Val Phe
          15                  20                  25

gca ggg gtg aag aag aga acc aaa gtc atc aag aac agc gtg aac cct      505
Ala Gly Val Lys Lys Arg Thr Lys Val Ile Lys Asn Ser Val Asn Pro
      30                  35                  40

gta tgg aat gag gga ttt gaa tgg gac ctc aag ggc atc ccc ctg gac      553
Val Trp Asn Glu Gly Phe Glu Trp Asp Leu Lys Gly Ile Pro Leu Asp
  45                  50                  55                  60

cag ggc tct gag ctt cat gtg gtg gtc aaa gac cat gag acg atg ggg      601
Gln Gly Ser Glu Leu His Val Val Val Lys Asp His Glu Thr Met Gly
                  65                  70                  75

agg aac agg ttc ctg ggg gaa gcc aag gtc cca ctc cga gag gtc ctc      649
Arg Asn Arg Phe Leu Gly Glu Ala Lys Val Pro Leu Arg Glu Val Leu
              80                  85                  90

gcc acc cct agt ctg tcc gcc agc ttc aat gcc ccc ctg ctg gac acc      697
Ala Thr Pro Ser Leu Ser Ala Ser Phe Asn Ala Pro Leu Leu Asp Thr
          95                  100                 105

aag aag cag ccc aca ggg gcc tcg ctg gtc ctg cag gtg tcc tac aca      745
Lys Lys Gln Pro Thr Gly Ala Ser Leu Val Leu Gln Val Ser Tyr Thr
      110                 115                 120
```

```
ccg ctg cct gga gct gtg ccc ctg ttc ccg ccc cct act cct ctg gag      793
Pro Leu Pro Gly Ala Val Pro Leu Phe Pro Pro Pro Thr Pro Leu Glu
125                 130                 135                 140

ccc tcc ccg act ctg cct gac ctg gat gta gtg gca gac aca gga gga      841
Pro Ser Pro Thr Leu Pro Asp Leu Asp Val Val Ala Asp Thr Gly Gly
                145                 150                 155

gag gaa gac aca gag gac cag gga ctc act gga gat gag gcg gag cca      889
Glu Glu Asp Thr Glu Asp Gln Gly Leu Thr Gly Asp Glu Ala Glu Pro
            160                 165                 170

ttc ctg gat caa agc gga ggc ccg ggg gct ccc acc acc cca agg aaa      937
Phe Leu Asp Gln Ser Gly Gly Pro Gly Ala Pro Thr Thr Pro Arg Lys
        175                 180                 185

cta cct tca cgt cct ccg ccc cac tac ccc ggg atc aaa aga aag cga      985
Leu Pro Ser Arg Pro Pro Pro His Tyr Pro Gly Ile Lys Arg Lys Arg
    190                 195                 200

agt gcg cct aca tct aga aag ctg ctg tca gac aaa ccg cag gat ttc     1033
Ser Ala Pro Thr Ser Arg Lys Leu Leu Ser Asp Lys Pro Gln Asp Phe
205                 210                 215                 220

cag atc agg gtc cag gtg atc gag ggg cgc cag ctg ccg ggg gtg aac     1081
Gln Ile Arg Val Gln Val Ile Glu Gly Arg Gln Leu Pro Gly Val Asn
                225                 230                 235

atc aag cct gtg gtc aag gtt acc gct gca ggg cag acc aag cgg acg     1129
Ile Lys Pro Val Val Lys Val Thr Ala Ala Gly Gln Thr Lys Arg Thr
            240                 245                 250

cgg atc cac aag gga aac agc cca ctc ttc aat gag act ctt ttc ttc     1177
Arg Ile His Lys Gly Asn Ser Pro Leu Phe Asn Glu Thr Leu Phe Phe
        255                 260                 265

aac ttg ttt gac tct cct ggg gag ctg ttt gat gag ccc atc ttt atc     1225
Asn Leu Phe Asp Ser Pro Gly Glu Leu Phe Asp Glu Pro Ile Phe Ile
    270                 275                 280

acg gtg gta gac tct cgt tct ctc agg aca gat gct ctc ctc ggg gag     1273
Thr Val Val Asp Ser Arg Ser Leu Arg Thr Asp Ala Leu Leu Gly Glu
285                 290                 295                 300

ttc cgg atg gac gtg ggc acc att tac aga gag ccc cgg cac gcc tat     1321
Phe Arg Met Asp Val Gly Thr Ile Tyr Arg Glu Pro Arg His Ala Tyr
                305                 310                 315

ctc agg aag tgg ctg ctg ctc tca gac cct gat gac ttc tct gct ggg     1369
Leu Arg Lys Trp Leu Leu Leu Ser Asp Pro Asp Asp Phe Ser Ala Gly
            320                 325                 330

gcc aga ggc tac ctg aaa aca agc ctt tgt gtg ctg ggg cct ggg gac     1417
Ala Arg Gly Tyr Leu Lys Thr Ser Leu Cys Val Leu Gly Pro Gly Asp
        335                 340                 345

gaa gcg cct ctg gag aga aaa gac ccc tct gaa gac aag gag gac att     1465
Glu Ala Pro Leu Glu Arg Lys Asp Pro Ser Glu Asp Lys Glu Asp Ile
    350                 355                 360

gaa agc aac ctg ctc cgg ccc aca ggc gta gcc ctg cga gga gcc cac     1513
Glu Ser Asn Leu Leu Arg Pro Thr Gly Val Ala Leu Arg Gly Ala His
365                 370                 375                 380

ttc tgc ctg aag gtc ttc cgg gcc gag gac ttg ccg cag atg gac gat     1561
Phe Cys Leu Lys Val Phe Arg Ala Glu Asp Leu Pro Gln Met Asp Asp
                385                 390                 395
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gcc gtg atg gac aac gtg aaa cag atc ttt ggc ttc gag agt aac aag      1609
Ala Val Met Asp Asn Val Lys Gln Ile Phe Gly Phe Glu Ser Asn Lys
            400                 405                 410

aag aac ttg gtg gac ccc ttt gtg gag gtc agc ttt gcg ggg aaa atg      1657
Lys Asn Leu Val Asp Pro Phe Val Glu Val Ser Phe Ala Gly Lys Met
        415                 420                 425

ctg tgc agc aag atc ttg gag aag acg gcc aac cct cag tgg aac cag      1705
Leu Cys Ser Lys Ile Leu Glu Lys Thr Ala Asn Pro Gln Trp Asn Gln
    430                 435                 440

aac atc aca ctg cct gcc atg ttt ccc tcc atg tgc gaa aaa atg agg      1753
Asn Ile Thr Leu Pro Ala Met Phe Pro Ser Met Cys Glu Lys Met Arg
445                 450                 455                 460

att cgt atc ata gac tgg gac cgc ctg act cac aat gac atc gtg gct      1801
Ile Arg Ile Ile Asp Trp Asp Arg Leu Thr His Asn Asp Ile Val Ala
                465                 470                 475

acc acc tac ctg agt atg tcg aaa atc tct gcc cct gga gga gaa ata      1849
Thr Thr Tyr Leu Ser Met Ser Lys Ile Ser Ala Pro Gly Gly Glu Ile
            480                 485                 490

gaa gag gag cct gca ggt gct gtc aag cct tcg aaa gcc tca gac ttg      1897
Glu Glu Glu Pro Ala Gly Ala Val Lys Pro Ser Lys Ala Ser Asp Leu
        495                 500                 505

gat gac tac ctg ggc ttc ctc ccc act ttt ggg ccc tgc tac atc aac      1945
Asp Asp Tyr Leu Gly Phe Leu Pro Thr Phe Gly Pro Cys Tyr Ile Asn
    510                 515                 520

ctc tat ggc agt ccc aga gag ttc aca ggc ttc cca gac ccc tac aca      1993
Leu Tyr Gly Ser Pro Arg Glu Phe Thr Gly Phe Pro Asp Pro Tyr Thr
525                 530                 535                 540

gag ctc aac aca ggc aag ggg gaa ggt gtg gct tat cgt ggc cgg ctt      2041
Glu Leu Asn Thr Gly Lys Gly Glu Gly Val Ala Tyr Arg Gly Arg Leu
                545                 550                 555

ctg ctc tcc ctg gag acc aag ctg gtg gag cac agt gaa cag aag gtg      2089
Leu Leu Ser Leu Glu Thr Lys Leu Val Glu His Ser Glu Gln Lys Val
            560                 565                 570

gag gac ctt cct gcg gat gac atc ctc cgg gtg gag aag tac ctt agg      2137
Glu Asp Leu Pro Ala Asp Asp Ile Leu Arg Val Glu Lys Tyr Leu Arg
        575                 580                 585

agg cgc aag tac tcc ctg ttt gcg gcc ttc tac tca gcc acc atg ctg      2185
Arg Arg Lys Tyr Ser Leu Phe Ala Ala Phe Tyr Ser Ala Thr Met Leu
    590                 595                 600

cag gat gtg gat gat gcc atc cag ttt gag gtc agc atc ggg aac tac      2233
Gln Asp Val Asp Asp Ala Ile Gln Phe Glu Val Ser Ile Gly Asn Tyr
605                 610                 615                 620

ggg aac aag ttc gac atg acc tgc ctg ccg ctg gcc tcc acc act cag      2281
Gly Asn Lys Phe Asp Met Thr Cys Leu Pro Leu Ala Ser Thr Thr Gln
                625                 630                 635

tac agc cgt gca gtc ttt gac ggg tgc cac tac tac tac cta ccc tgg      2329
Tyr Ser Arg Ala Val Phe Asp Gly Cys His Tyr Tyr Tyr Leu Pro Trp
            640                 645                 650
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ggt aac gtg aaa cct gtg gtg gtg ctg tca tcc tac tgg gag gac atc      2377
Gly Asn Val Lys Pro Val Val Val Leu Ser Ser Tyr Trp Glu Asp Ile
        655                 660                 665

agc cat aga atc gag act cag aac cag ctg ctt ggg att gct gac cgg      2425
Ser His Arg Ile Glu Thr Gln Asn Gln Leu Leu Gly Ile Ala Asp Arg
    670                 675                 680

ctg gaa gct ggc ctg gag cag gtc cac ctg gcc ctg aag gcg cag tgc      2473
Leu Glu Ala Gly Leu Glu Gln Val His Leu Ala Leu Lys Ala Gln Cys
685                 690                 695                 700

tcc acg gag gac gtg gac tcg ctg gtg gct cag ctg acg gat gag ctc      2521
Ser Thr Glu Asp Val Asp Ser Leu Val Ala Gln Leu Thr Asp Glu Leu
                705                 710                 715

atc gca ggc tgc agc cag cct ctg ggt gac atc cat gag aca ccc tct      2569
Ile Ala Gly Cys Ser Gln Pro Leu Gly Asp Ile His Glu Thr Pro Ser
            720                 725                 730

gcc acc cac ctg gac cag tac ctg tac cag ctg cgc acc cat cac ctg      2617
Ala Thr His Leu Asp Gln Tyr Leu Tyr Gln Leu Arg Thr His His Leu
        735                 740                 745

agc caa atc act gag gct gcc ctg gcc ctg aag ctc ggc cac agt gag      2665
Ser Gln Ile Thr Glu Ala Ala Leu Ala Leu Lys Leu Gly His Ser Glu
    750                 755                 760

ctc cct gca gct ctg gag cag gcg gag gac tgg ctc ctg cgt ctg cgt      2713
Leu Pro Ala Ala Leu Glu Gln Ala Glu Asp Trp Leu Leu Arg Leu Arg
765                 770                 775                 780

gcc ctg gca gag gag ccc cag aac agc ctg ccg gac atc gtc atc tgg      2761
Ala Leu Ala Glu Glu Pro Gln Asn Ser Leu Pro Asp Ile Val Ile Trp
                785                 790                 795

atg ctg cag gga gac aag cgt gtg gca tac cag cgg gtg ccc gcc cac      2809
Met Leu Gln Gly Asp Lys Arg Val Ala Tyr Gln Arg Val Pro Ala His
            800                 805                 810

caa gtc ctc ttc tcc cgg cgg ggt gcc aac tac tgt ggc aag aat tgt      2857
Gln Val Leu Phe Ser Arg Arg Gly Ala Asn Tyr Cys Gly Lys Asn Cys
        815                 820                 825

ggg aag cta cag aca atc ttt ctg aaa tat ccg atg gag aag gtg cct      2905
Gly Lys Leu Gln Thr Ile Phe Leu Lys Tyr Pro Met Glu Lys Val Pro
    830                 835                 840

ggc gcc cgg atg cca gtg cag ata cgg gtc aag ctg tgg ttt ggg ctc      2953
Gly Ala Arg Met Pro Val Gln Ile Arg Val Lys Leu Trp Phe Gly Leu
845                 850                 855                 860

tct gtg gat gag aag gag ttc aac cag ttt gct gag ggg aag ctg tct      3001
Ser Val Asp Glu Lys Glu Phe Asn Gln Phe Ala Glu Gly Lys Leu Ser
                865                 870                 875

gtc ttt gct gaa acc tat gag aac gag act aag ttg gcc ctt gtt ggg      3049
Val Phe Ala Glu Thr Tyr Glu Asn Glu Thr Lys Leu Ala Leu Val Gly
            880                 885                 890

aac tgg ggc aca acg ggc ctc acc tac ccc aag ttt tct gac gtc acg      3097
Asn Trp Gly Thr Thr Gly Leu Thr Tyr Pro Lys Phe Ser Asp Val Thr
        895                 900                 905

ggc aag atc aag cta ccc aag gac agc ttc cgc ccc tcg gcc ggc tgg      3145
Gly Lys Ile Lys Leu Pro Lys Asp Ser Phe Arg Pro Ser Ala Gly Trp
    910                 915                 920
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acc tgg gct gga gat tgg ttc gtg tgt ccg gag aag act ctg ctc cat      3193
Thr Trp Ala Gly Asp Trp Phe Val Cys Pro Glu Lys Thr Leu Leu His
925                 930                 935                 940

gac atg gac gcc ggt cac ctg agc ttc gtg gaa gag gtg ttt gag aac      3241
Asp Met Asp Ala Gly His Leu Ser Phe Val Glu Glu Val Phe Glu Asn
                945                 950                 955

cag acc cgg ctt ccc gga ggc cag tgg atc tac atg agt gac aac tac      3289
Gln Thr Arg Leu Pro Gly Gly Gln Trp Ile Tyr Met Ser Asp Asn Tyr
            960                 965                 970

acc gat gtg aac ggg gag aag gtg ctt ccc aag gat gac att gag tgc      3337
Thr Asp Val Asn Gly Glu Lys Val Leu Pro Lys Asp Asp Ile Glu Cys
        975                 980                 985

cca ctg ggc tgg aag tgg gaa gat gag gaa tgg tcc aca gac ctc aac      3385
Pro Leu Gly Trp Lys Trp Glu Asp Glu Glu Trp Ser Thr Asp Leu Asn
    990                 995                 1000

cgg gct gtc gat gag caa ggc tgg gag tat agc atc acc atc ccc ccg      3433
Arg Ala Val Asp Glu Gln Gly Trp Glu Tyr Ser Ile Thr Ile Pro Pro
1005                1010                1015                1020

gag cgg aag ccg aag cac tgg gtc cct gct gag aag atg tac tac aca      3481
Glu Arg Lys Pro Lys His Trp Val Pro Ala Glu Lys Met Tyr Tyr Thr
                1025                1030                1035

cac cga cgg cgg cgc tgg gtg cgc ctg cgc agg agg gat ctc agc caa      3529
His Arg Arg Arg Arg Trp Val Arg Leu Arg Arg Arg Asp Leu Ser Gln
            1040                1045                1050

atg gaa gca ctg aaa agg cac agg cag gcg gag gcg gag ggc gag ggc      3577
Met Glu Ala Leu Lys Arg His Arg Gln Ala Glu Ala Glu Gly Glu Gly
        1055                1060                1065

tgg gag tac gcc tct ctt ttt ggc tgg aag ttc cac ctc gag tac cgc      3625
Trp Glu Tyr Ala Ser Leu Phe Gly Trp Lys Phe His Leu Glu Tyr Arg
    1070                1075                1080

aag aca gat gcc ttc cgc cgc cgc cgc tgg cgc cgt cgc atg gag cca      3673
Lys Thr Asp Ala Phe Arg Arg Arg Arg Trp Arg Arg Arg Met Glu Pro
1085                1090                1095                1100

ctg gag aag acg ggg cct gca gct gtg ttt gcc ctt gag ggg gcc ctg      3721
Leu Glu Lys Thr Gly Pro Ala Ala Val Phe Ala Leu Glu Gly Ala Leu
                1105                1110                1115

ggc ggc gtg atg gat gac aag agt gaa gat tcc atg tcc gtc tcc acc      3769
Gly Gly Val Met Asp Asp Lys Ser Glu Asp Ser Met Ser Val Ser Thr
            1120                1125                1130

ttg agc ttc ggt gtg aac aga ccc acg att tcc tgc ata ttc gac tat      3817
Leu Ser Phe Gly Val Asn Arg Pro Thr Ile Ser Cys Ile Phe Asp Tyr
        1135                1140                1145

ggg aac cgc tac cat cta cgc tgc tac atg tac cag gcc cgg gac ctg      3865
Gly Asn Arg Tyr His Leu Arg Cys Tyr Met Tyr Gln Ala Arg Asp Leu
    1150                1155                1160

gct gcg atg gac aag gac tct ttt tct gat ccc tat gcc atc gtc tcc      3913
Ala Ala Met Asp Lys Asp Ser Phe Ser Asp Pro Tyr Ala Ile Val Ser
1165                1170                1175                1180
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ttc ctg cac cag agc cag aag acg gtg gtg gtg aag aac acc ctt aac     3961
Phe Leu His Gln Ser Gln Lys Thr Val Val Val Lys Asn Thr Leu Asn
                1185                1190                1195

ccc acc tgg gac cag acg ctc atc ttc tac gag atc gag atc ttt ggc     4009
Pro Thr Trp Asp Gln Thr Leu Ile Phe Tyr Glu Ile Glu Ile Phe Gly
            1200                1205                1210

gag ccg gcc aca gtt gct gag caa ccg ccc agc att gtg gtg gag ctg     4057
Glu Pro Ala Thr Val Ala Glu Gln Pro Pro Ser Ile Val Val Glu Leu
        1215                1220                1225

tac gac cat gac act tat ggt gca gac gag ttt atg ggt cgc tgc atc     4105
Tyr Asp His Asp Thr Tyr Gly Ala Asp Glu Phe Met Gly Arg Cys Ile
    1230                1235                1240

tgt caa ccg agt ctg gaa cgg atg cca cgg ctg gcc tgg ttc cca ctg     4153
Cys Gln Pro Ser Leu Glu Arg Met Pro Arg Leu Ala Trp Phe Pro Leu
1245                1250                1255                1260

acg agg ggc agc cag ccg tcg ggg gag ctg ctg gcc tct ttt gag ctc     4201
Thr Arg Gly Ser Gln Pro Ser Gly Glu Leu Leu Ala Ser Phe Glu Leu
                1265                1270                1275

atc cag aga gag aag ccg gcc atc cac cat att cct ggt ttt gag gtg     4249
Ile Gln Arg Glu Lys Pro Ala Ile His His Ile Pro Gly Phe Glu Val
            1280                1285                1290

cag gag aca tca agg atc ctg gat gag tct gag gac aca gac ctg ccc     4297
Gln Glu Thr Ser Arg Ile Leu Asp Glu Ser Glu Asp Thr Asp Leu Pro
        1295                1300                1305

tac cca cca ccc cag agg gag gcc aac atc tac atg gtt cct cag aac     4345
Tyr Pro Pro Pro Gln Arg Glu Ala Asn Ile Tyr Met Val Pro Gln Asn
    1310                1315                1320

atc aag cca gcg ctc cag cgt acc gcc atc gag atc ctg gca tgg ggc     4393
Ile Lys Pro Ala Leu Gln Arg Thr Ala Ile Glu Ile Leu Ala Trp Gly
1325                1330                1335                1340

ctg cgg aac atg aag agt tac cag ctg gcc aac atc tcc tcc ccc agc     4441
Leu Arg Asn Met Lys Ser Tyr Gln Leu Ala Asn Ile Ser Ser Pro Ser
                1345                1350                1355

ctc gtg gta gag tgt ggg ggc cag acg gtg cag tcc tgt gtc atc agg     4489
Leu Val Val Glu Cys Gly Gly Gln Thr Val Gln Ser Cys Val Ile Arg
            1360                1365                1370

aac ctc cgg aag aac ccc aac ttt gac atc tgc acc ctc ttc atg gaa     4537
Asn Leu Arg Lys Asn Pro Asn Phe Asp Ile Cys Thr Leu Phe Met Glu
        1375                1380                1385

gtg atg ctg ccc agg gag gag ctc tac tgc ccc ccc atc acc gtc aag     4585
Val Met Leu Pro Arg Glu Glu Leu Tyr Cys Pro Pro Ile Thr Val Lys
    1390                1395                1400

gtc atc gat aac cgc cag ttt ggc cgc cgg cct gtg gtg ggc cag tgt     4633
Val Ile Asp Asn Arg Gln Phe Gly Arg Arg Pro Val Val Gly Gln Cys
1405                1410                1415                1420

acc atc cgc tcc ctg gag agc ttc ctg tgt gac ccc tac tcg gcg gag     4681
Thr Ile Arg Ser Leu Glu Ser Phe Leu Cys Asp Pro Tyr Ser Ala Glu
                1425                1430                1435

agt cca tcc cca cag ggt ggc cca gac gat gtg agc cta ctc agt cct     4729
Ser Pro Ser Pro Gln Gly Gly Pro Asp Asp Val Ser Leu Leu Ser Pro
            1440                1445                1450
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ggg gaa gac gtg ctc atc gac att gat gac aag gag ccc ctc atc ccc      4777
Gly Glu Asp Val Leu Ile Asp Ile Asp Asp Lys Glu Pro Leu Ile Pro
        1455                1460                1465

atc cag gag gaa gag ttc atc gat tgg tgg agc aaa ttc ttt gcc tcc      4825
Ile Gln Glu Glu Glu Phe Ile Asp Trp Trp Ser Lys Phe Phe Ala Ser
    1470                1475                1480

ata ggg gag agg gaa aag tgc ggc tcc tac ctg gag aag gat ttt gac      4873
Ile Gly Glu Arg Glu Lys Cys Gly Ser Tyr Leu Glu Lys Asp Phe Asp
1485                1490                1495                1500

acc ctg aag gtc tat gac aca cag ctg gag aat gtg gag gcc ttt gag      4921
Thr Leu Lys Val Tyr Asp Thr Gln Leu Glu Asn Val Glu Ala Phe Glu
                1505                1510                1515

ggc ctg tct gac ttt tgt aac acc ttc aag ctg tac cgg ggc aag acg      4969
Gly Leu Ser Asp Phe Cys Asn Thr Phe Lys Leu Tyr Arg Gly Lys Thr
            1520                1525                1530

cag gag gag aca gaa gat cca tct gtg att ggt gaa ttt aag ggc ctc      5017
Gln Glu Glu Thr Glu Asp Pro Ser Val Ile Gly Glu Phe Lys Gly Leu
        1535                1540                1545

ttc aaa att tat ccc ctc cca gaa gac cca gcc atc ccc atg ccc cca      5065
Phe Lys Ile Tyr Pro Leu Pro Glu Asp Pro Ala Ile Pro Met Pro Pro
    1550                1555                1560

aga cag ttc cac cag ctg gcc gcc cag gga ccc cag gag tgc ttg gtc      5113
Arg Gln Phe His Gln Leu Ala Ala Gln Gly Pro Gln Glu Cys Leu Val
1565                1570                1575                1580

cgt atc tac att gtc cga gca ttt ggc ctg cag ccc aag gac ccc aat      5161
Arg Ile Tyr Ile Val Arg Ala Phe Gly Leu Gln Pro Lys Asp Pro Asn
                1585                1590                1595

gga aag tgt gat cct tac atc aag atc tcc ata ggg aag aaa tca gtg      5209
Gly Lys Cys Asp Pro Tyr Ile Lys Ile Ser Ile Gly Lys Lys Ser Val
            1600                1605                1610

agt gac cag gat aac tac atc ccc tgc acg ctg gag ccc gta ttt gga      5257
Ser Asp Gln Asp Asn Tyr Ile Pro Cys Thr Leu Glu Pro Val Phe Gly
        1615                1620                1625

aag atg ttc gag ctg acc tgc act ctg cct ctg gag aag gac cta aag      5305
Lys Met Phe Glu Leu Thr Cys Thr Leu Pro Leu Glu Lys Asp Leu Lys
    1630                1635                1640

atc act ctc tat gac tat gac ctc ctc tcc aag gac gaa aag atc ggt      5353
Ile Thr Leu Tyr Asp Tyr Asp Leu Leu Ser Lys Asp Glu Lys Ile Gly
1645                1650                1655                1660

gag acg gtc gtc gac ctg gag aac agg ctg ctg tcc aag ttt ggg gct      5401
Glu Thr Val Val Asp Leu Glu Asn Arg Leu Leu Ser Lys Phe Gly Ala
                1665                1670                1675

cgc tgt gga ctc cca cag acc tac tgt gtc tct gga ccg aac cag tgg      5449
Arg Cys Gly Leu Pro Gln Thr Tyr Cys Val Ser Gly Pro Asn Gln Trp
            1680                1685                1690

cgg gac cag ctc cgc ccc tcc cag ctc ctc cac ctc ttc tgc cag cag      5497
Arg Asp Gln Leu Arg Pro Ser Gln Leu Leu His Leu Phe Cys Gln Gln
        1695                1700                1705
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cat aga gtc aag gca cct gtg tac cgg aca gac cgt gta atg ttt cag      5545
His Arg Val Lys Ala Pro Val Tyr Arg Thr Asp Arg Val Met Phe Gln
    1710                1715                1720

gat aaa gaa tat tcc att gaa gag ata gag gct ggc agg atc cca aac      5593
Asp Lys Glu Tyr Ser Ile Glu Glu Ile Glu Ala Gly Arg Ile Pro Asn
1725                1730                1735                1740

cca cac ctg ggc cca gtg gag gag cgt ctg gct ctg cat gtg ctt cag      5641
Pro His Leu Gly Pro Val Glu Glu Arg Leu Ala Leu His Val Leu Gln
                1745                1750                1755

cag cag ggc ctg gtc ccg gag cac gtg gag tca cgg ccc ctc tac agc      5689
Gln Gln Gly Leu Val Pro Glu His Val Glu Ser Arg Pro Leu Tyr Ser
            1760                1765                1770

ccc ctg cag cca gac atc gag cag ggg aag ctg cag atg tgg gtc gac      5737
Pro Leu Gln Pro Asp Ile Glu Gln Gly Lys Leu Gln Met Trp Val Asp
        1775                1780                1785

cta ttt ccg aag gcc ctg ggg cgg cct gga cct ccc ttc aac atc acc      5785
Leu Phe Pro Lys Ala Leu Gly Arg Pro Gly Pro Pro Phe Asn Ile Thr
    1790                1795                1800

cca cgg aga gcc aga agg ttt ttc ctg cgt tgt att atc tgg aat acc      5833
Pro Arg Arg Ala Arg Arg Phe Phe Leu Arg Cys Ile Ile Trp Asn Thr
1805                1810                1815                1820

aga gat gtg atc ctg gat gac ctg agc ctc acg ggg gag aag atg agc      5881
Arg Asp Val Ile Leu Asp Asp Leu Ser Leu Thr Gly Glu Lys Met Ser
                1825                1830                1835

gac att tat gtg aaa ggt tgg atg att ggc ttt gaa gaa cac aag caa      5929
Asp Ile Tyr Val Lys Gly Trp Met Ile Gly Phe Glu Glu His Lys Gln
            1840                1845                1850

aag aca gac gtg cat tat cgt tcc ctg gga ggt gaa ggc aac ttc aac      5977
Lys Thr Asp Val His Tyr Arg Ser Leu Gly Gly Glu Gly Asn Phe Asn
        1855                1860                1865

tgg agg ttc att ttc ccc ttc gac tac ctg cca gct gag caa gtc tgt      6025
Trp Arg Phe Ile Phe Pro Phe Asp Tyr Leu Pro Ala Glu Gln Val Cys
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acc att gcc aag aag gat gcc ttc tgg agg ctg gac aag act gag agc      6073
Thr Ile Ala Lys Lys Asp Ala Phe Trp Arg Leu Asp Lys Thr Glu Ser
1885                1890                1895                1900

aaa atc cca gca cga gtg gtg ttc cag atc tgg gac aat gac aag ttc      6121
Lys Ile Pro Ala Arg Val Val Phe Gln Ile Trp Asp Asn Asp Lys Phe
                1905                1910                1915

tcc ttt gat gat ttt ctg ggc tcc ctg cag ctc gat ctc aac cgc atg      6169
Ser Phe Asp Asp Phe Leu Gly Ser Leu Gln Leu Asp Leu Asn Arg Met
            1920                1925                1930

ccc aag cca gcc aag aca gcc aag aag tgc tcc ttg gac cag ctg gat      6217
Pro Lys Pro Ala Lys Thr Ala Lys Lys Cys Ser Leu Asp Gln Leu Asp
        1935                1940                1945

gat gct ttc cac cca gaa tgg ttt gtg tcc ctt ttt gag cag aaa aca      6265
Asp Ala Phe His Pro Glu Trp Phe Val Ser Leu Phe Glu Gln Lys Thr
    1950                1955                1960

gtg aag ggc tgg tgg ccc tgt gta gca gaa gag ggt gag aag aaa ata      6313
Val Lys Gly Trp Trp Pro Cys Val Ala Glu Glu Gly Glu Lys Lys Ile
1965                1970                1975                1980
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ctg gcg ggc aag ctg gaa atg acc ttg gag att gta gca gag agt gag      6361
Leu Ala Gly Lys Leu Glu Met Thr Leu Glu Ile Val Ala Glu Ser Glu
                1985                1990                1995

cat gag gag cgg cct gct ggc cag ggc cgg gat gag ccc aac atg aac      6409
His Glu Glu Arg Pro Ala Gly Gln Gly Arg Asp Glu Pro Asn Met Asn
            2000                2005                2010

cct aag ctt gag gac cca agg cgc ccc gac acc tcc ttc ctg tgg ttt      6457
Pro Lys Leu Glu Asp Pro Arg Arg Pro Asp Thr Ser Phe Leu Trp Phe
        2015                2020                2025

acc tcc cca tac aag acc atg aag ttc atc ctg tgg cgg cgt ttc cgg      6505
Thr Ser Pro Tyr Lys Thr Met Lys Phe Ile Leu Trp Arg Arg Phe Arg
    2030                2035                2040

tgg gcc atc atc ctc ttc atc atc ctc ttc atc ctg ctg ctg ttc ctg      6553
Trp Ala Ile Ile Leu Phe Ile Ile Leu Phe Ile Leu Leu Leu Phe Leu
2045                2050                2055                2060

gcc atc ttc atc tac gcc ttc ccg aac tat gct gcc atg aag ctg gtg      6601
Ala Ile Phe Ile Tyr Ala Phe Pro Asn Tyr Ala Ala Met Lys Leu Val
                2065                2070                2075

aag ccc ttc agc tgaggactct cctgccctgt agaaggggcc gtggggtccc          6653
Lys Pro Phe Ser
            2080

ctccagcatg ggactggcct gcctcctccg cccagctcgg cgagctcctc cagacctcct   6713
aggcctgatt gtcctgccag ggtgggcaga cagacagatg gaccggccca cactcccaga   6773
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Thr Asp Ile Ser Asp Ala Tyr Cys Ser Ala Val Phe Ala Gly Val Lys
             20                  25                  30
Lys Arg Thr Lys Val Ile Lys Asn Ser Val Asn Pro Val Trp Asn Glu
         35                  40                  45
Gly Phe Glu Trp Asp Leu Lys Gly Ile Pro Leu Asp Gln Gly Ser Glu
     50                  55                  60
Leu His Val Val Val Lys Asp His Glu Thr Met Gly Arg Asn Arg Phe
 65                  70                  75                  80
Leu Gly Glu Ala Lys Val Pro Leu Arg Glu Val Leu Ala Thr Pro Ser
                 85                  90                  95
Leu Ser Ala Ser Phe Asn Ala Pro Leu Leu Asp Thr Lys Lys Gln Pro
            100                 105                 110
Thr Gly Ala Ser Leu Val Leu Gln Val Ser Tyr Thr Pro Leu Pro Gly
        115                 120                 125
Ala Val Pro Leu Phe Pro Pro Pro Thr Pro Leu Glu Pro Ser Pro Thr
    130                 135                 140
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ccccctcta tccagcttac acttctagtt ttgagagttt 220

<210> 47
<211> 172
<212> DNA
<213> Homo sapiens

<400> 47
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ttctttacgc ttcagaggag cctgcaggtg ctgtcaagcc ttcgaaagcc tcagactgta 120
cgttgctgtc accttgggga caaccagggg agtggggcct tgggttttgg ct 172

<210> 48
<211> 200
<212> DNA
<213> Homo sapiens

<400> 48
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acccctacac agagctcaac acaggcaagg taagccggct ggagccctgg caagggcagg 180
atgccacatg cccaggtggg 200

<210> 49
<211> 217
<212> DNA
<213> Homo sapiens

<400> 49
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cttatcgtgg ccggcttctg ctctccctgg agaccaagct ggtggagcac agtgaacaga 120
aggtggagga ccttcctgcg gatgacatcc tccgggtgga ggtgaggggt gtggctctgg 180

gtgggagctg ggcgtcgggg cagggaaggg atggcca 217

<210> 50
<211> 269
<212> DNA
<213> Homo sapiens

<400> 50
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ggatgtggat gatgccatcc agtttgaggt cagcatcggg aactacggga acaagttcga 180
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ggcagtgctc ctggctggga ccccgatca 269

<210> 51
<211> 225
<212> DNA
<213> Homo sapiens

<400> 51
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gaatcgagac tcagaaccag ctgcttggga ttgctgaccg gctggtgagt gaaaacttgc 180
ccaaagctgc acatgcctat gcatgcacct gctacccccg ctgca 225

<210> 52
<211> 227
<212> DNA
<213> Homo sapiens

<400> 52
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gtggactcgc tggtggctca gctgacggat gagctcatcg caggctgcag gtaggggga 180
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<211> 303
<212> DNA
<213> Homo sapiens

<400> 53
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aac 303

<210> 54
<211> 272
<212> DNA
<213> Homo sapiens

<400> 54
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gtgcccgccc accaagtcct cttctcccgg cggggtgcca actactgtgg caagaattgt 180
gggaagctac agacaatctt tctgaaagtg agttttcttt ttccaagtca tgatcgtatt 240
tccaacataa ggcctttctc ccatctcttg ct 272

<210> 55
<211> 219
<212> DNA
<213> Homo sapiens

<400> 55
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aaccagtttg ctgaggggaa gctgtctgtc tttgctgaaa ccgtgagtac ctgccagccc 180
ccacctctgc ctcccactac ctggagctgc cttggcccc 219

<210> 56
<211> 292
<212> DNA
<213> Homo sapiens

<400> 56
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accccaagtt ttctgacgtc acgggcaaga tcaagctacc caaggacagc ttccgccct 180
cggccggctg gacctgggct ggagattggt tcgtgtgtcc ggagaagacg tgagtcgtgg 240
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<210> 57
<211> 242
<212> DNA
<213> Homo sapiens

<400> 57
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ctccatgaca tggacgccgg tcacctgagc ttcgtggaag aggtgtttga gaaccagacc 120
cggcttcccg gaggccagtg gatctacatg agtgacaact acaccgatgt ggtaaagcag 180
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ca 242

<210> 58
<211> 215
<212> DNA
<213> Homo sapiens

<400> 58
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tggtccacag acctcaaccg ggctgtcgat gagcaaggtg ggcagcatgt ggaacctggc 180
gagccccatc cccggcaagc tctcaagcca tgcat 215

<210> 59
<211> 246
<212> DNA
<213> Homo sapiens

<400> 59
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ctgctgagaa gatgtactac acacaccgac ggcggcgctg ggtgcgcctg cgcaggaggg 180
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gcctgt 246

<210> 60
<211> 253
<212> DNA
<213> Homo sapiens

<400> 60
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cagatgcctt ccgccgccgc cgctggcgcc gtcgcatgga gccactggag aagacggggc 180
ctgcagctgt gtttgccctt gagggggccc tggtatgtgg ggctgcactt gtcctggctt 240
gggtagggta tat 253

<210> 61
<211> 177

<212> DNA
<213> Homo sapiens

<400> 61
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ttccatgtcc gtctccacct tgagcttcgg tgtgaacaga cccacgattt cctgcatatt 120
cgactgtaag taggcttcga ggcctctatg gggtgataag ggtgtgtcac cttatgc 177

<210> 62
<211> 181
<212> DNA
<213> Homo sapiens

<400> 62
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ctaccatcta cgctgctaca tgtaccaggc ccgggacctg gctgcgatgg acaaggactc 120
tttttctggt aggtgggaga gaggcaggag agtcagagac tgtgggctga gatctgggaa 180
t 181

<210> 63
<211> 319
<212> DNA
<213> Homo sapiens

<400> 63
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ccctctggcc atgcagatcc ctatgccatc gtctccttcc tgcaccagag ccagaagacg 120
gtggtggtga agaacaccct taaccccacc tgggaccaga cgctcatctt ctacgagatc 180
gagatctttg gcgagccggc cacagttgct gagcaaccgc ccagcattgt ggtggagctg 240
tacgaccatg acacttatgt gagtctgccc agctcctgcc tcgtcccctc acagggaggg 300
accatgtgca aaggtgggg 319

<210> 64
<211> 249
<212> DNA
<213> Homo sapiens

<400> 64
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ttatgggtcg ctgcatctgt caaccgagtc tggaacggat gccacggctg gcctggttcc 120
cactgacgag gggcagccag ccgtcggggg agctgctggc ctcttttgag ctcatccaga 180
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ggccaaccc 249

<210> 65
<211> 158
<212> DNA
<213> Homo sapiens

<400> 65
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ccagagctct cttttcttca ctccagccgg ccatccacca tattcctggt tttgaggtaa 120
gtcttgctct gacctttcct tcttcaaact gattgcca 158

<210> 66
<211> 132
<212> DNA
<213> Homo sapiens

<400> 66
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caggtgcagg agacatcaag gatcctggat gaggtgagct ggcggggccg aggtagaggg 120
aaggtgaagc ca 132

<210> 67
<211> 216
<212> DNA

<213> Homo sapiens

<400> 67
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ccagcgctcc agcgtaccgc catcgaggtg agccgtccgg gcctgggcgt gggggctggg 180
agcagcctgc ccttcccctt cctggcccca gccttt 216

<210> 68
<211> 263
<212> DNA
<213> Homo sapiens

<400> 68
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gggggccaga cggtgcagtc ctgtgtcatc aggaacctcc ggaagaaccc caactttgac 180
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ctggggctag aagttctaca tgt 263

<210> 69
<211> 249
<212> DNA
<213> Homo sapiens

<400> 69
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gtgtaccatc cgctccctgg agagcttcct gtgtgacccc tactcggcgg agagtccatc 180
cccacagggt ggcccaggta ggggaagggg agatgatggg caggtcaggg aaggggagc 240
ctagggcaa 249

<210> 70
<211> 180
<212> DNA
<213> Homo sapiens

<400> 70
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atgtgagcct actcagtcct ggggaagacg tgctcatcga cattgatgac aaggagcccc 120
tcatccccat ccaggtagga tgggcatcct ccagggaggc ctgggtcacc tttcccctcc 180

<210> 71
<211> 211
<212> DNA
<213> Homo sapiens

<400> 71
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gagttcatcg attggtggag caaattcttt gcctccatag gggagaggga aaagtgcggc 120
tcctacctgg agaaggattt tgacaccctg aaggtaaggc ctctcttcag tctgacagtc 180
ggtgtgtgtg tgcgtgctgg gcagtgggag a 211

<210> 72
<211> 235
<212> DNA
<213> Homo sapiens

<400> 72
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acacacagct ggagaatgtg gaggcctttg agggcctgtc tgacttttgt aacaccttca 120
agctgtaccg gggcaagacg caggaggaga cagaagatcc atctgtgatt ggtgaattta 180
aggtaaatcc tcgaagacgt ccctaaccca ggtgggccta agactgtggt gttgg 235

<210> 73
<211> 268
<212> DNA

<213> Homo sapiens

<400> 73
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acagttccac cagctggccg cccagggacc ccaggagtgc ttggtccgta tctacattgt 180
ccgagcattt ggcctgcagc ccaaggaccc caatggaaag gtaactttct agagccctca 240
cctccccaga gtagcaggct caggtaca 268

<210> 74
<211> 200
<212> DNA
<213> Homo sapiens

<400> 74
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gatctccata gggaagaaat cagtgagtga ccaggataac tacatcccct gcacgctgga 120
gcccgtattt ggaaagtaaa ttggggcatc ttgggtcttg gggtggagga gccagacagg 180
ataacccaca gtctagtggg 200

<210> 75
<211> 263
<212> DNA
<213> Homo sapiens

<400> 75
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ggggctggct gcctgcttct ctg 263

<210> 76
<211> 237
<212> DNA
<213> Homo sapiens

<400> 76
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cagctccgcc cctcccagct cctccacctc ttctgccagc agcatagagt caaggcacct 120
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gagctgccac atgaccccaa accatggtgg gctctcgctg tatccctccc tctctca 237

<210> 77
<211> 245
<212> DNA
<213> Homo sapiens

<400> 77
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gcagggcctg gtcccggagc acgtggagtc acggcccctc tacagccccc tgcagccaga 180
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ccagg 245

<210> 78
<211> 214
<212> DNA
<213> Homo sapiens

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ggggaagctg gggaagctgc agatgtgggt cgacctattt ccgaaggccc tggggcggcc 120
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ctgagctggg ctgaggggtg gggcgttgca gcct 214

<210> 79
<211> 229
<212> DNA
<213> Homo sapiens

<400> 79
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gcctcacggg ggagaagatg agcgacattt atgtgaaagg gtagggagcc agcgtcctct 180
tgcctgtcca gcttcccgca gctcccgtgc tccctctggg ttgtgcaca 229

<210> 80
<211> 261
<212> DNA
<213> Homo sapiens

<400> 80
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gggaggtgaa ggcaacttca actggaggtt cattttcccc ttcgactacc tgccagctga 180
gcaagtctgt accattgcca agaaggtcag tgtccttccg attccctgtg gtgccagcac 240
cagggcttct aaagttagcc t 261

<210> 81
<211> 234
<212> DNA
<213> Homo sapiens

<400> 81
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cttctggagg ctggacaaga ctgagagcaa aatcccagca cgagtggtgt tccagatctg 120
ggacaatgac aagttctcct ttgatgattt tctggtgatt ttctgggtaa gcgctattgc 180
tagaatccca ttctgcacat gggggctgcc ccagaaccca cactgtgtgt ttat 234

<210> 82
<211> 297
<212> DNA
<213> Homo sapiens

<400> 82
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<210> 83
<211> 237
<212> DNA
<213> Homo sapiens

<400> 83
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cagtgcccag cccctgagcc ccaatgccca caggtctggg ggtataggca cagtcca 237

<210> 84
<211> 252
<212> DNA
<213> Homo sapiens

<400> 84
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tgggccatca tcctcttcat catcctcttc atcctgctgc tgttcctggc catcttcatc 180
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gggagttcat ca 252

<210> 85
<211> 391
<212> DNA
<213> Homo sapiens

<400> 85
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aaccacaaaa aaaaaaaaaa aaaaaaaaaa a 391

<210> 86
<211> 51
<212> PRT
<213> Homo sapiens

<400> 86
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1 5 10 15
Glu Gly Phe Glu Trp Asp Leu Lys Gly Ile Pro Leu Asp Gln Gly Ser
20 25 30
Glu Leu His Val Val Val Lys Asp His Glu Thr Met Gly Arg Asn Arg
35 40 45
Phe Leu Gly
50

<210> 87
<211> 45
<212> PRT
<213> Homo sapiens

<400> 87
Ser Lys Ile Leu Glu Lys Thr Ala Asn Pro Gln Trp Asn Gln Asn Ile
1 5 10 15
Thr Leu Pro Ala Met Phe Pro Ser Met Cys Glu Lys Met Arg Ile Arg
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Ile Ile Asp Trp Asp Arg Leu Thr His Asn Asp Ile Val
35 40 45

<210> 88
<211> 82
<212> PRT
<213> Homo sapiens

<400> 88
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Tyr Ala Ile Val Ser Phe Leu His Gln Ser Gln Lys Thr Val Val Val
20 25 30
Lys Asn Thr Leu Asn Pro Thr Trp Asp Gln Thr Leu Ile Phe Tyr Glu
35 40 45
Ile Glu Ile Phe Gly Glu Pro Ala Thr Val Ala Glu Gln Pro Pro Ser
50 55 60
Ile Val Val Glu Leu Tyr Asp His Asp Thr Tyr Gly Ala Asp Glu Phe
65 70 75 80
Met Gly

<210> 89
<211> 79
<212> PRT
<213> Homo sapiens

<400> 89

Ile Tyr Ile Val Arg Ala Phe Gly Leu Gln Pro Lys Asp Pro Asn Gly
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Lys Cys Asp Pro Tyr Ile Lys Ile Ser Ile Gly Lys Lys Ser Val Ser
20 25 30
Asp Gln Asp Asn Tyr Ile Pro Cys Thr Leu Glu Pro Val Phe Gly Lys
35 40 45
Met Phe Glu Leu Thr Cys Thr Leu Pro Leu Glu Lys Asp Leu Lys Ile
50 55 60
Thr Leu Tyr Asp Tyr Asp Leu Leu Ser Lys Asp Glu Lys Ile Gly
65 70 75

<210> 90
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<212> DNA
<213> Homo sapiens

<400> 90

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gggaggtgaa ggcaacttca actggaggtt ca 152

<210> 91
<211> 56
<212> DNA
<213> Homo sapiens

<400> 91

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<210> 92
<211> 55
<212> DNA
<213> Homo sapiens

<400> 92

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<210> 93
<211> 68
<212> DNA
<213> Homo sapiens

<400> 93

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gtgtttat 68

<210> 94
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<212> DNA
<213> Homo sapiens

<400> 94

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<210> 95
<211> 62
<212> DNA
<213> Homo sapiens

<400> 95

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gt 62

<210> 96
<211> 68
<212> DNA

<213> Homo sapiens

<400> 96
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cccctcag 68

<210> 97
<211> 59
<212> DNA
<213> Homo sapiens

<400> 97
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<210> 98
<211> 44
<212> DNA
<213> Homo sapiens

<400> 98
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<210> 99
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attacaggca tgagtcactg tgcccggcag agatggtcta attcatatga aagaactctg 240

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ctaaccttgt ggaatttttt ttttttgaga agcaaattgc aaatttgtga tagatctaaa     360
ggagattgac taagagggtg accatctgga aatgacgtca tgtgagaatg gttaaag atg    420
                                                                  Met
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ctc ggg aga ttg agc cta gag aaa gga aga ttt gtg aac cca gga ggc       468
Leu Gly Arg Leu Ser Leu Glu Lys Gly Arg Phe Val Asn Pro Gly Gly
                5                  10                  15

aga ggt aga gat cca gga gag ggc ggc gtg atg gat gac aag agt gaa       516
Arg Gly Arg Asp Pro Gly Glu Gly Gly Val Met Asp Asp Lys Ser Glu
            20                  25                  30

gat tcc atg tcc gtc tcc acc ttg agc ttc ggt gtg aac aga ccc acg       564
Asp Ser Met Ser Val Ser Thr Leu Ser Phe Gly Val Asn Arg Pro Thr
        35                  40                  45

att tcc tgc ata ttc gac tat ggg aac cgc tac cat cta cgc tgc tac       612
Ile Ser Cys Ile Phe Asp Tyr Gly Asn Arg Tyr His Leu Arg Cys Tyr
    50                  55                  60                  65

atg tac cag gcc cgg gac ctg gct gcg atg gac aag gac tct ttt tct       660
Met Tyr Gln Ala Arg Asp Leu Ala Ala Met Asp Lys Asp Ser Phe Ser
                70                  75                  80

gat ccc tat gcc atc gtc tcc ttc ctg cac cag agc cag aag acg gtg       708
Asp Pro Tyr Ala Ile Val Ser Phe Leu His Gln Ser Gln Lys Thr Val
            85                  90                  95

gtg gtg aag aac acc ctt aac ccc acc tgg gac cag acg ctc atc ttc       756
Val Val Lys Asn Thr Leu Asn Pro Thr Trp Asp Gln Thr Leu Ile Phe
        100                 105                 110

tac gag atc gag atc ttt ggc gag ccg gcc aca gtt gct gag caa ccg       804
Tyr Glu Ile Glu Ile Phe Gly Glu Pro Ala Thr Val Ala Glu Gln Pro
    115                 120                 125

ccc agc att gtg gtg gag ctg tac gac cat gac act tat ggt gca gac       852
Pro Ser Ile Val Val Glu Leu Tyr Asp His Asp Thr Tyr Gly Ala Asp
130                 135                 140                 145

gag ttt atg ggt cgc tgc atc tgt caa ccg agt ctg gaa cgg atg cca       900
Glu Phe Met Gly Arg Cys Ile Cys Gln Pro Ser Leu Glu Arg Met Pro
                150                 155                 160

cgg ctg gcc tgg ttc cca ctg acg agg ggc agc cag ccg tcg ggg gag       948
Arg Leu Ala Trp Phe Pro Leu Thr Arg Gly Ser Gln Pro Ser Gly Glu
            165                 170                 175

ctg ctg gcc tct ttt gag ctc atc cag aga gag aag ccg gcc atc cac       996
Leu Leu Ala Ser Phe Glu Leu Ile Gln Arg Glu Lys Pro Ala Ile His
        180                 185                 190

cat att cct ggt ttt gag gtg cag gag aca tca agg atc ctg gat gag      1044
His Ile Pro Gly Phe Glu Val Gln Glu Thr Ser Arg Ile Leu Asp Glu
    195                 200                 205

tct gag gac aca gac ctg ccc tac cca cca ccc cag agg gag gcc aac      1092
Ser Glu Asp Thr Asp Leu Pro Tyr Pro Pro Pro Gln Arg Glu Ala Asn
210                 215                 220                 225

atc tac atg gtt cct cag aac atc aag cca gcg ctc cag cgt acc gcc      1140
Ile Tyr Met Val Pro Gln Asn Ile Lys Pro Ala Leu Gln Arg Thr Ala
                230                 235                 240
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atc gag atc ctg gca tgg ggc ctg cgg aac atg aag agt tac cag ctg      1188
Ile Glu Ile Leu Ala Trp Gly Leu Arg Asn Met Lys Ser Tyr Gln Leu
            245                 250                 255

gcc aac atc tcc tcc ccc agc ctc gtg gta gag tgt ggg ggc cag acg      1236
Ala Asn Ile Ser Ser Pro Ser Leu Val Val Glu Cys Gly Gly Gln Thr
        260                 265                 270

gtg cag tcc tgt gtc atc agg aac ctc cgg aag aac ccc aac ttt gac      1284
Val Gln Ser Cys Val Ile Arg Asn Leu Arg Lys Asn Pro Asn Phe Asp
    275                 280                 285

atc tgc acc ctc ttc atg gaa gtg atg ctg ccc agg gag gag ctc tac      1332
Ile Cys Thr Leu Phe Met Glu Val Met Leu Pro Arg Glu Glu Leu Tyr
290                 295                 300                 305

tgc ccc ccc atc acc gtc aag gtc atc gat aac cgc cag ttt ggc cgc      1380
Cys Pro Pro Ile Thr Val Lys Val Ile Asp Asn Arg Gln Phe Gly Arg
                310                 315                 320

cgg cct gtg gtg ggc cag tgt acc atc cgc tcc ctg gag agc ttc ctg      1428
Arg Pro Val Val Gly Gln Cys Thr Ile Arg Ser Leu Glu Ser Phe Leu
            325                 330                 335

tgt gac ccc tac tcg gcg gag agt cca tcc cca cag ggt ggc cca gac      1476
Cys Asp Pro Tyr Ser Ala Glu Ser Pro Ser Pro Gln Gly Gly Pro Asp
        340                 345                 350

gat gtg agc cta ctc agt cct ggg gaa gac gtg ctc atc gac att gat      1524
Asp Val Ser Leu Leu Ser Pro Gly Glu Asp Val Leu Ile Asp Ile Asp
    355                 360                 365

gac aag gag ccc ctc atc ccc atc cag gag gaa gag ttc atc gat tgg      1572
Asp Lys Glu Pro Leu Ile Pro Ile Gln Glu Glu Glu Phe Ile Asp Trp
370                 375                 380                 385

tgg agc aaa ttc ttt gcc tcc ata ggg gag agg gaa aag tgc ggc tcc      1620
Trp Ser Lys Phe Phe Ala Ser Ile Gly Glu Arg Glu Lys Cys Gly Ser
                390                 395                 400

tac ctg gag aag gat ttt gac acc ctg aag gtc tat gac aca cag ctg      1668
Tyr Leu Glu Lys Asp Phe Asp Thr Leu Lys Val Tyr Asp Thr Gln Leu
            405                 410                 415

gag aat gtg gag gcc ttt gag ggc ctg tct gac ttt tgt aac acc ttc      1716
Glu Asn Val Glu Ala Phe Glu Gly Leu Ser Asp Phe Cys Asn Thr Phe
        420                 425                 430

aag ctg tac cgg ggc aag acg cag gag gag aca gaa gat cca tct gtg      1764
Lys Leu Tyr Arg Gly Lys Thr Gln Glu Glu Thr Glu Asp Pro Ser Val
    435                 440                 445

att ggt gaa ttt aag ggc ctc ttc aaa att tat ccc ctc cca gaa gac      1812
Ile Gly Glu Phe Lys Gly Leu Phe Lys Ile Tyr Pro Leu Pro Glu Asp
450                 455                 460                 465

cca gcc atc ccc atg ccc cca aga cag ttc cac cag ctg gcc gcc cag      1860
Pro Ala Ile Pro Met Pro Pro Arg Gln Phe His Gln Leu Ala Ala Gln
                470                 475                 480

gga ccc cag gag tgc ttg gtc cgt atc tac att gtc cga gca ttt ggc      1908
Gly Pro Gln Glu Cys Leu Val Arg Ile Tyr Ile Val Arg Ala Phe Gly
            485                 490                 495

ctg cag ccc aag gac ccc aat gga aag tgt gat cct tac atc aag atc      1956
Leu Gln Pro Lys Asp Pro Asn Gly Lys Cys Asp Pro Tyr Ile Lys Ile
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Ser Ile Gly Lys Lys Ser Val Ser Asp Gln Asp Asn Tyr Ile Pro Cys
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acg ctg gag ccc gta ttt gga aag atg ttc gag ctg acc tgc act ctg      2052
Thr Leu Glu Pro Val Phe Gly Lys Met Phe Glu Leu Thr Cys Thr Leu
530                 535                 540                 545

cct ctg gag aag gac cta aag atc act ctc tat gac tat gac ctc ctc      2100
Pro Leu Glu Lys Asp Leu Lys Ile Thr Leu Tyr Asp Tyr Asp Leu Leu
                550                 555                 560

tcc aag gac gaa aag atc ggt gag acg gtc gtc gac ctg gag aac agg      2148
Ser Lys Asp Glu Lys Ile Gly Glu Thr Val Val Asp Leu Glu Asn Arg
            565                 570                 575

ctg ctg tcc aag ttt ggg gct cgc tgt gga ctc cca cag acc tac tgt      2196
Leu Leu Ser Lys Phe Gly Ala Arg Cys Gly Leu Pro Gln Thr Tyr Cys
        580                 585                 590

gtc tct gga ccg aac cag tgg cgg gac cag ctc cgc ccc tcc cag ctc      2244
Val Ser Gly Pro Asn Gln Trp Arg Asp Gln Leu Arg Pro Ser Gln Leu
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ctc cac ctc ttc tgc cag cag cat aga gtc aag gca cct gtg tac cgg      2292
Leu His Leu Phe Cys Gln Gln His Arg Val Lys Ala Pro Val Tyr Arg
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aca gac cgt gta atg ttt cag gat aaa gaa tat tcc att gaa gag ata      2340
Thr Asp Arg Val Met Phe Gln Asp Lys Glu Tyr Ser Ile Glu Glu Ile
                630                 635                 640

gag gct ggc agg atc cca aac cca cac ctg ggc cca gtg gag gag cgt      2388
Glu Ala Gly Arg Ile Pro Asn Pro His Leu Gly Pro Val Glu Glu Arg
            645                 650                 655

ctg gct ctg cat gtg ctt cag cag cag ggc ctg gtc ccg gag cac gtg      2436
Leu Ala Leu His Val Leu Gln Gln Gln Gly Leu Val Pro Glu His Val
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gag tca cgg ccc ctc tac agc ccc ctg cag cca gac atc gag cag ggg      2484
Glu Ser Arg Pro Leu Tyr Ser Pro Leu Gln Pro Asp Ile Glu Gln Gly
    675                 680                 685

aag ctg cag atg tgg gtc gac cta ttt ccg aag gcc ctg ggg cgg cct      2532
Lys Leu Gln Met Trp Val Asp Leu Phe Pro Lys Ala Leu Gly Arg Pro
690                 695                 700                 705

gga cct ccc ttc aac atc acc cca cgg aga gcc aga agg ttt ttc ctg      2580
Gly Pro Pro Phe Asn Ile Thr Pro Arg Arg Ala Arg Arg Phe Phe Leu
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cgt tgt att atc tgg aat acc aga gat gtg atc ctg gat gac ctg agc      2628
Arg Cys Ile Ile Trp Asn Thr Arg Asp Val Ile Leu Asp Asp Leu Ser
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ctc acg ggg gag aag atg agc gac att tat gtg aaa ggt tgg atg att      2676
Leu Thr Gly Glu Lys Met Ser Asp Ile Tyr Val Lys Gly Trp Met Ile
        740                 745                 750

ggc ttt gaa gaa cac aag caa aag aca gac gtg cat tat cgt tcc ctg      2724
Gly Phe Glu Glu His Lys Gln Lys Thr Asp Val His Tyr Arg Ser Leu
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ctg cca gct gag caa gtc tgt acc att gcc aag aag gat gcc ttc tgg      2820
Leu Pro Ala Glu Gln Val Cys Thr Ile Ala Lys Lys Asp Ala Phe Trp
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agg ctg gac aag act gag agc aaa atc cca gca cga gtg gtg ttc cag      2868
Arg Leu Asp Lys Thr Glu Ser Lys Ile Pro Ala Arg Val Val Phe Gln
            805                 810                 815

atc tgg gac aat gac aag ttc tcc ttt gat gat ttt ctg ggc tcc ctg      2916
Ile Trp Asp Asn Asp Lys Phe Ser Phe Asp Asp Phe Leu Gly Ser Leu
        820                 825                 830

cag ctc gat ctc aac cgc atg ccc aag cca gcc aag aca gcc aag aag      2964
Gln Leu Asp Leu Asn Arg Met Pro Lys Pro Ala Lys Thr Ala Lys Lys
    835                 840                 845

tgc tcc ttg gac cag ctg gat gat gct ttc cac cca gaa tgg ttt gtg      3012
Cys Ser Leu Asp Gln Leu Asp Asp Ala Phe His Pro Glu Trp Phe Val
850                 855                 860                 865

tcc ctt ttt gag cag aaa aca gtg aag ggc tgg tgg ccc tgt gta gca      3060
Ser Leu Phe Glu Gln Lys Thr Val Lys Gly Trp Trp Pro Cys Val Ala
                870                 875                 880

gaa gag ggt gag aag aaa ata ctg gcg ggc aag ctg gaa atg acc ttg      3108
Glu Glu Gly Glu Lys Lys Ile Leu Ala Gly Lys Leu Glu Met Thr Leu
            885                 890                 895

gag att gta gca gag agt gag cat gag gag cgg cct gct ggc cag ggc      3156
Glu Ile Val Ala Glu Ser Glu His Glu Glu Arg Pro Ala Gly Gln Gly
        900                 905                 910

cgg gat gag ccc aac atg aac cct aag ctt gag gac cca agg cgc ccc      3204
Arg Asp Glu Pro Asn Met Asn Pro Lys Leu Glu Asp Pro Arg Arg Pro
    915                 920                 925

gac acc tcc ttc ctg tgg ttt acc tcc cca tac aag acc atg aag ttc      3252
Asp Thr Ser Phe Leu Trp Phe Thr Ser Pro Tyr Lys Thr Met Lys Phe
930                 935                 940                 945

atc ctg tgg cgg cgt ttc cgg tgg gcc atc atc ctc ttc atc atc ctc      3300
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                950                 955                 960

ttc atc ctg ctg ctg ttc ctg gcc atc ttc atc tac gcc ttc ccg aac      3348
Phe Ile Leu Leu Leu Phe Leu Ala Ile Phe Ile Tyr Ala Phe Pro Asn
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Tyr Ala Ala Met Lys Leu Val Lys Pro Phe Ser
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Thr Ile Ser Cys Ile Phe Asp Tyr Gly Asn Arg Tyr His Leu Arg Cys
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Tyr Met Tyr Gln Ala Arg Asp Leu Ala Ala Met Asp Lys Asp Ser Phe
65 70 75 80
Ser Asp Pro Tyr Ala Ile Val Ser Phe Leu His Gln Ser Gln Lys Thr
85 90 95
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Phe Tyr Glu Ile Glu Ile Phe Gly Glu Pro Ala Thr Val Ala Glu Gln
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Pro Pro Ser Ile Val Val Glu Leu Tyr Asp His Asp Thr Tyr Gly Ala
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Glu Leu Leu Ala Ser Phe Glu Leu Ile Gln Arg Glu Lys Pro Ala Ile
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His His Ile Pro Gly Phe Glu Val Gln Glu Thr Ser Arg Ile Leu Asp
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Glu Ser Glu Asp Thr Asp Leu Pro Tyr Pro Pro Pro Gln Arg Glu Ala
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225 230 235 240
Ala Ile Glu Ile Leu Ala Trp Gly Leu Arg Asn Met Lys Ser Tyr Gln
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Leu Ala Asn Ile Ser Ser Pro Ser Leu Val Val Glu Cys Gly Gly Gln
260 265 270
Thr Val Gln Ser Cys Val Ile Arg Asn Leu Arg Lys Asn Pro Asn Phe
275 280 285
Asp Ile Cys Thr Leu Phe Met Glu Val Met Leu Pro Arg Glu Glu Leu
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Tyr Cys Pro Pro Ile Thr Val Lys Val Ile Asp Asn Arg Gln Phe Gly
305 310 315 320
Arg Arg Pro Val Val Gly Gln Cys Thr Ile Arg Ser Leu Glu Ser Phe
325 330 335
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Asp Asp Lys Glu Pro Leu Ile Pro Ile Gln Glu Glu Glu Phe Ile Asp
370 375 380
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385 390 395 400
Ser Tyr Leu Glu Lys Asp Phe Asp Thr Leu Lys Val Tyr Asp Thr Gln
405 410 415
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420 425 430
Phe Lys Leu Tyr Arg Gly Lys Thr Gln Glu Glu Thr Glu Asp Pro Ser
435 440 445
Val Ile Gly Glu Phe Lys Gly Leu Phe Lys Ile Tyr Pro Leu Pro Glu
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Asp Pro Ala Ile Pro Met Pro Pro Arg Gln Phe His Gln Leu Ala Ala
465 470 475 480
Gln Gly Pro Gln Glu Cys Leu Val Arg Ile Tyr Ile Val Arg Ala Phe
485 490 495
Gly Leu Gln Pro Lys Asp Pro Asn Gly Lys Cys Asp Pro Tyr Ile Lys
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Ile Ser Ile Gly Lys Lys Ser Val Ser Asp Gln Asp Asn Tyr Ile Pro
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Cys Thr Leu Glu Pro Val Phe Gly Lys Met Phe Glu Leu Thr Cys Thr
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Arg Leu Leu Ser Lys Phe Gly Ala Arg Cys Gly Leu Pro Gln Thr Tyr
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Ile Gly Phe Glu Glu His Lys Gln Lys Thr Asp Val His Tyr Arg Ser
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770 775 780
Tyr Leu Pro Ala Glu Gln Val Cys Thr Ile Ala Lys Lys Asp Ala Phe
785 790 795 800
Trp Arg Leu Asp Lys Thr Glu Ser Lys Ile Pro Ala Arg Val Val Phe
805 810 815
Gln Ile Trp Asp Asn Asp Lys Phe Ser Phe Asp Asp Phe Leu Gly Ser
820 825 830
Leu Gln Leu Asp Leu Asn Arg Met Pro Lys Pro Ala Lys Thr Ala Lys
835 840 845
Lys Cys Ser Leu Asp Gln Leu Asp Asp Ala Phe His Pro Glu Trp Phe
850 855 860
Val Ser Leu Phe Glu Gln Lys Thr Val Lys Gly Trp Trp Pro Cys Val
865 870 875 880
Ala Glu Glu Gly Glu Lys Lys Ile Leu Ala Gly Lys Leu Glu Met Thr
885 890 895
Leu Glu Ile Val Ala Glu Ser Glu His Glu Glu Arg Pro Ala Gly Gln
900 905 910
Gly Arg Asp Glu Pro Asn Met Asn Pro Lys Leu Glu Asp Pro Arg Arg
915 920 925
Pro Asp Thr Ser Phe Leu Trp Phe Thr Ser Pro Tyr Lys Thr Met Lys
930 935 940
Phe Ile Leu Trp Arg Arg Phe Arg Trp Ala Ile Ile Leu Phe Ile Ile
945 950 955 960
Leu Phe Ile Leu Leu Leu Phe Leu Ala Ile Phe Ile Tyr Ala Phe Pro
965 970 975
Asn Tyr Ala Ala Met Lys Leu Val Lys Pro Phe Ser
980 985

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19395

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :C12N 15/11, 15/00; C07K 16/00
US CL : 536/23.1, 435/440, 530/387.1

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 536/23.1, 435/440, 530/387.1

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

BIOSIS, CAPLUS, EMBASE, ESBIOBASE, LIFESCI, MEDLINE, SCISEARCH, TOXLIT
Search Terms: dysferlin, lgmd2b

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WEILER et al. Limb-girdle muscular dystrophy and Myoshi Myopathy in an aboriginal Canadian kindred map to LGMD2B and segregate with the same haplotype. American Journal of Human Genetics. October 1996, Vol.59, pages 872-878, especially page 873.	32,35
X	KOENIG et al. Complete cloning of the Duchenne Muscular Dystrophy (DMD) cDNA and preliminary genomic organization of the DMD gene in normal and affected individuals. Cell. 31 July 1987, Vol. 50, pages 509-517, especially pages 511-513.	32-33,36

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 17 NOVEMBER 1999	Date of mailing of the international search report 13 JAN 2000
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-4242	Authorized officer Stephen Siu Telephone No. (703) 308-0196

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19395

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X,P --- Y,P	Database GenCore version 4.5, Compugen Ltd., No. AI128455, 'NCI-CGAP, National Cancer Institute, Cancer Genome Anatomy Project (CGAP), Tumor Gene Index', Unpublished, 27 October 1998	1,6,12 ----- 7,14,16
X --- Y	Database GenCore version 4.5, Compugen Ltd., No. R41062, WAYE, M.M.Y. et al. 'Gene expression of adult human heart as revealed by random sequencing of cDNA library,' Miami Winter Biotechnol. Symp. Proc. 6,90 , 16 May 16, 1995.	1, 6, 11-12 ----- 7, 14
X --- Y	Database GenCore version 4.5, Compugen Ltd., No. AA718275, Marra et al, 'The WashU-HHMI Mouse EST Project', Unpublished, 29 December 1997.	1, 6, 11-12 ---------- 7, 14
Y	BASHIR et al. Genetic and physical mapping at the limb-girdle muscular dystrophy locus (LGMD2B) on chromosome 2p. Genomics. April 1996, Vol.33, pages 46-52, especially page 47.	32,36
Y	MOREIRA et al. The seventh form of autosomal recessive limb-girdle muscular dystrophy is mapped to 17q11-12. American Journal of Human Genetics. July 1997, Vol. 61, pages 151-159, entire document.	32, 35
Y	Database GenCore version 4.5, Compugen Ltd., No. R76778, HILLIER et al., 'The WashU-Merck EST Project', Unpublished, 06 June 1995.	7, 14
A,E	AHLBERG et al. Genetic Linkage of Welander Distal Myopathy to chromosome 2p13. Annals of Neurology. September 1999, Vol. 46, No.3, pages 399-404, especially page 400.	37, 39
A,E	BITTNER et al. Dysferlin deletion in SJL mice (SJL-Dysf) defines a natural model for limb girdle muscular dystrophy 2B. Nature Genetics. October 1999, Vol. 23, pages 141-142, especially page 141.	40
A,P	BASHIR et al. A gene related to Caenorhabditis elegans spermatogenesis factor fer-1 is mutated in limb-girdle muscular dystrophy type 2B. Nature Genetics. September 1998, Vol 20, pages 37-42.	1-53
A,E	Matsuda et al. Dysferlin is a surface membrane-associated protein that is absent in Miyoshi Myopathy. Neurology 22 September 1999, Vol. 53, No. 5, pages 1119-1122, especially pages 1119-1120.	40

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US99/19395

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A,P	LIU et al. Dysferlin, a novel skeletal muscle gene, is mutated in Miyoshi Myopathy and limb girdle muscular dystrophy. Nature Genetics. September 1998, Vol. 20, pages 31-36.	1-54